



**NIEHS**

National Institute of  
Environmental Health Sciences

**AAAAI Keynote Session**

# **Human Disease: A Sum Game of Genes and the Environment**

**March 06, 2006**

**David A. Schwartz, M.D.**  
**Director**  
**National Institute of Environmental  
Health Sciences**



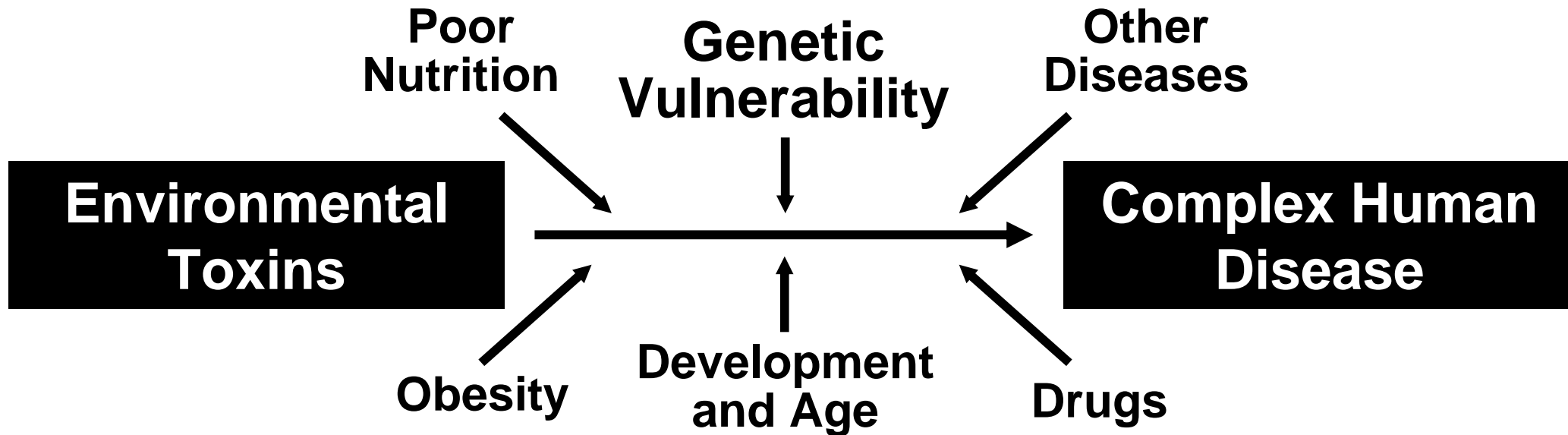
U.S. Department of Health and Human Services  
National Institute of Health  
National Institute of Environmental Health Sciences

# **Human Disease: A Sum Game of Genes and the Environment**

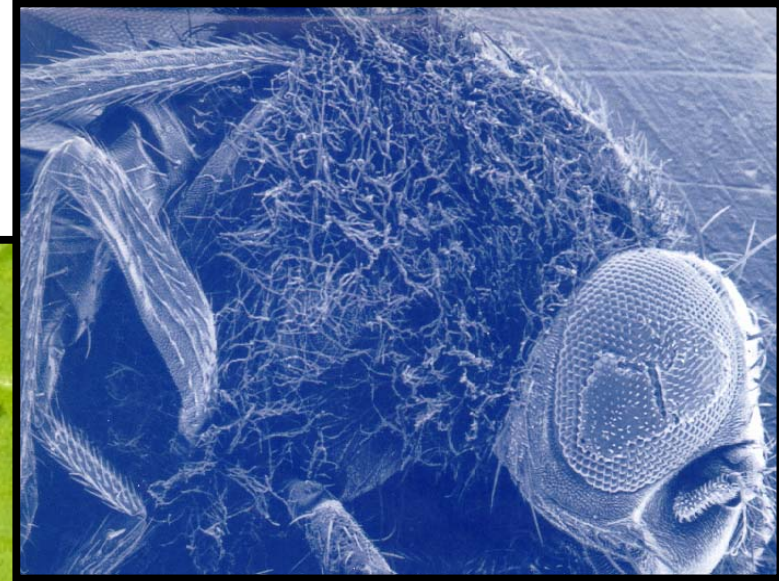


- **Scientific Approaches to Environmental Genomics**
- **Infrastructure Needs**
- **Priorities for Program Development**

# Why do certain people develop disease when challenged with an environmental toxin while others remain healthy?



# Scientific Approaches to Environmental Genetics and Genomics



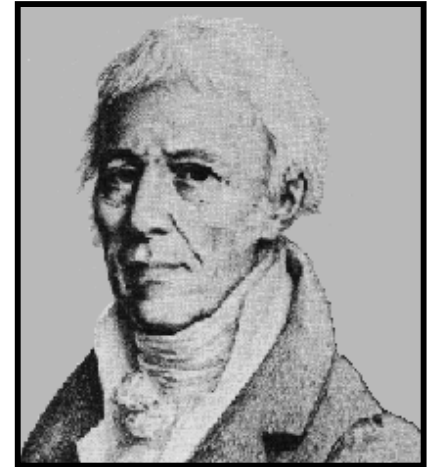


# Environmental Epigenetics

*Lamarckism Revisited*



**Inheritance of  
Acquired Traits**



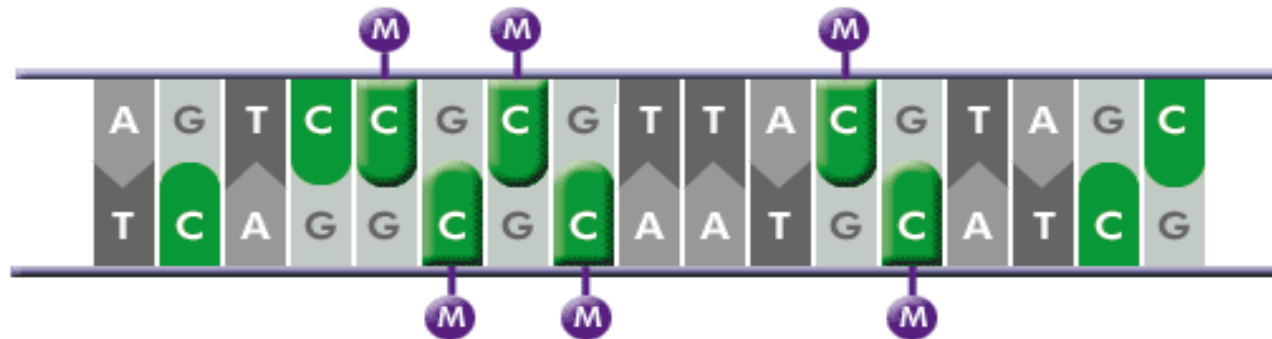
**1744-1829**



# Mechanisms of Epigenetic Inheritance

*Inheritance not dependent on DNA sequence*

- **DNA Methylation** – silences gene by methylating the cytosine of a CpG motif



# Mechanisms of Epigenetic Inheritance

*Inheritance not dependent on DNA sequence*

- **DNA Methylation** – silences gene by methylating the cytosine of a CpG motif
- **Genomic Imprinting** – differential methylation results in preferential silencing of maternal or paternal allele
- **Histone Modification** – methylation, acetylation, or phosphorylation of histone can regulate transcription of genes

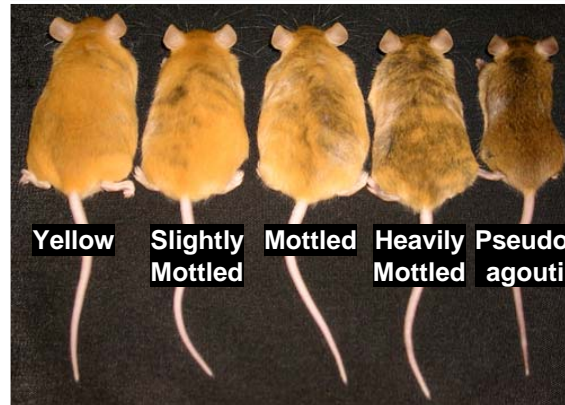
# **Proof of Concept: Agouti Mice**



# Proof of Concept: Agouti Mice

Coat color in Agouti mice varies from black to yellow due to stochastic methylation of CpG motifs

Unmethylated *agouti*  
(expressed)



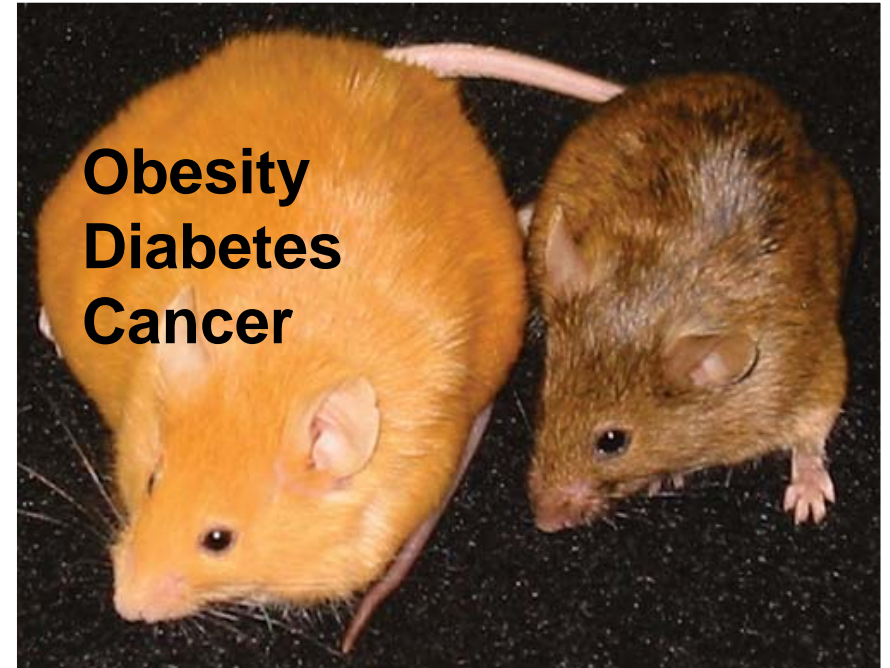
Methylated *agouti*  
(not expressed)

**Mol Cell Biol**  
**August, 2003**  
**Volume 23**



**Folate and B12 have  
transgenerational effect on  
decreased expression of the  
Agouti gene**

Bob Waterland and Randy Jirtle

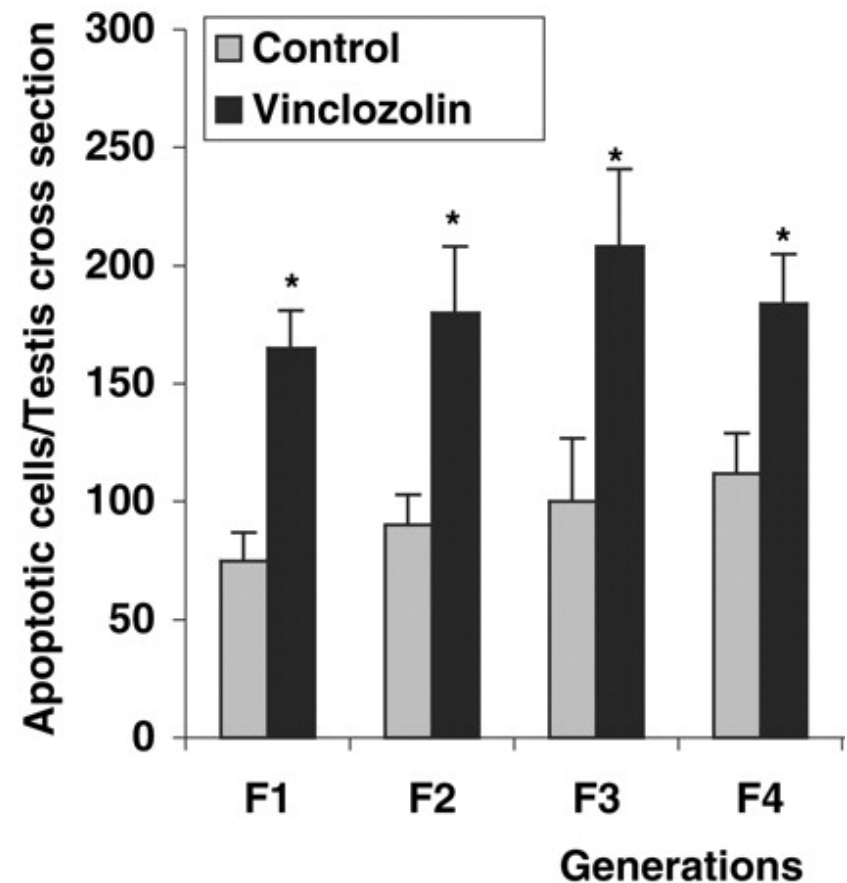


**Waterland. *Mol Cell Biol* 2003; 23:5293**



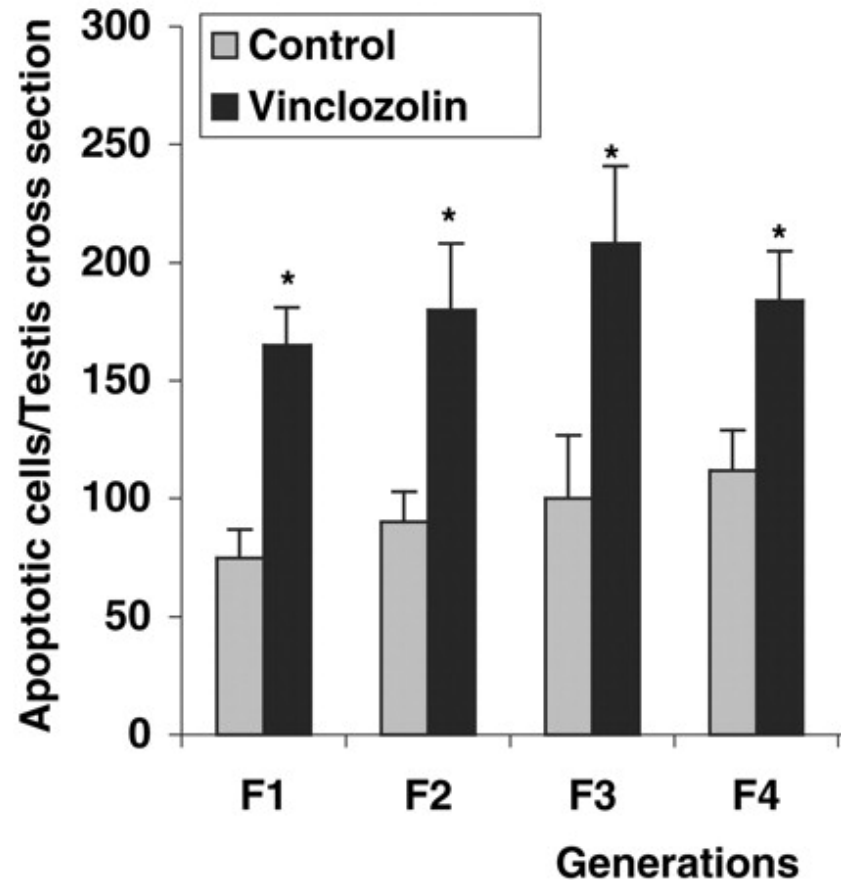
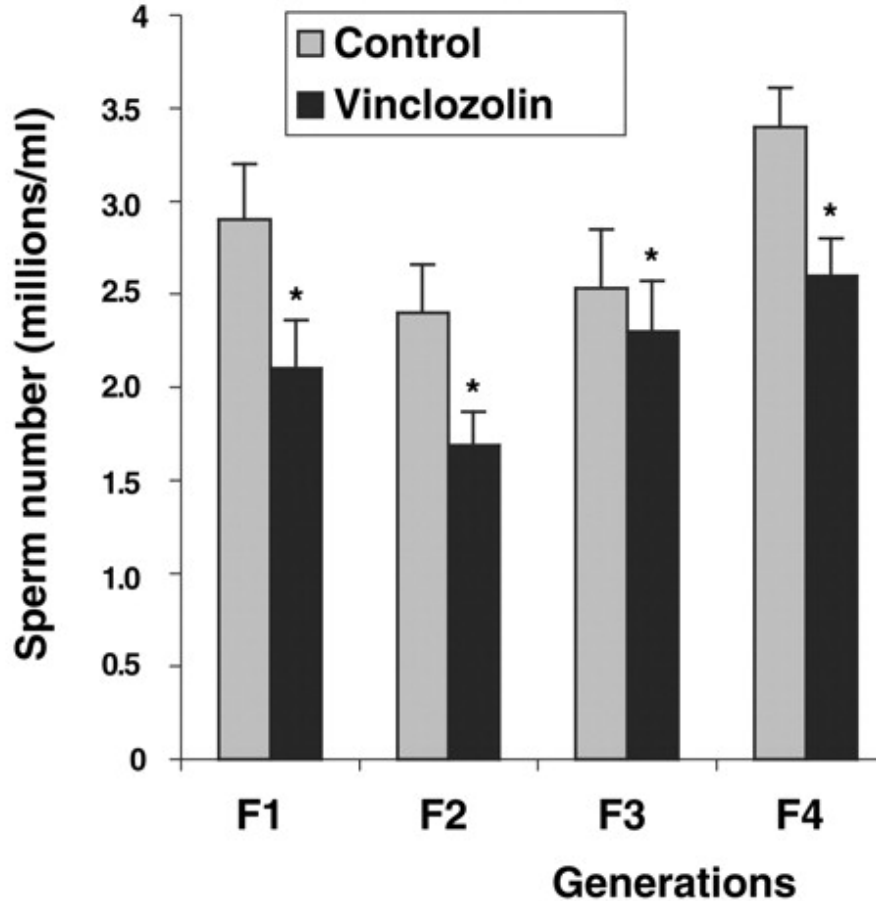
**Endocrine disruptors have  
transgenerational effects  
on male fertility that occur  
as a result of DNA  
methylation**

Matt Anway et al.



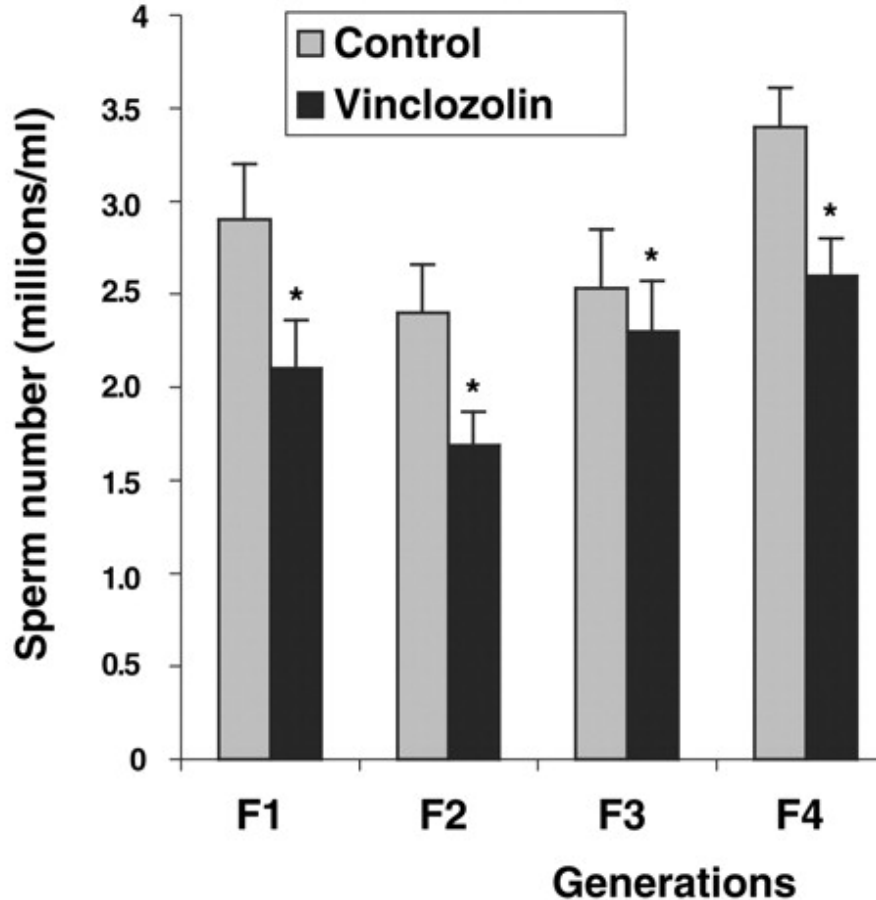
**Anway. *Science* 2005; 308:1466**

# Environmental Epigenetics



Anway. *Science* 2005; 308:1466

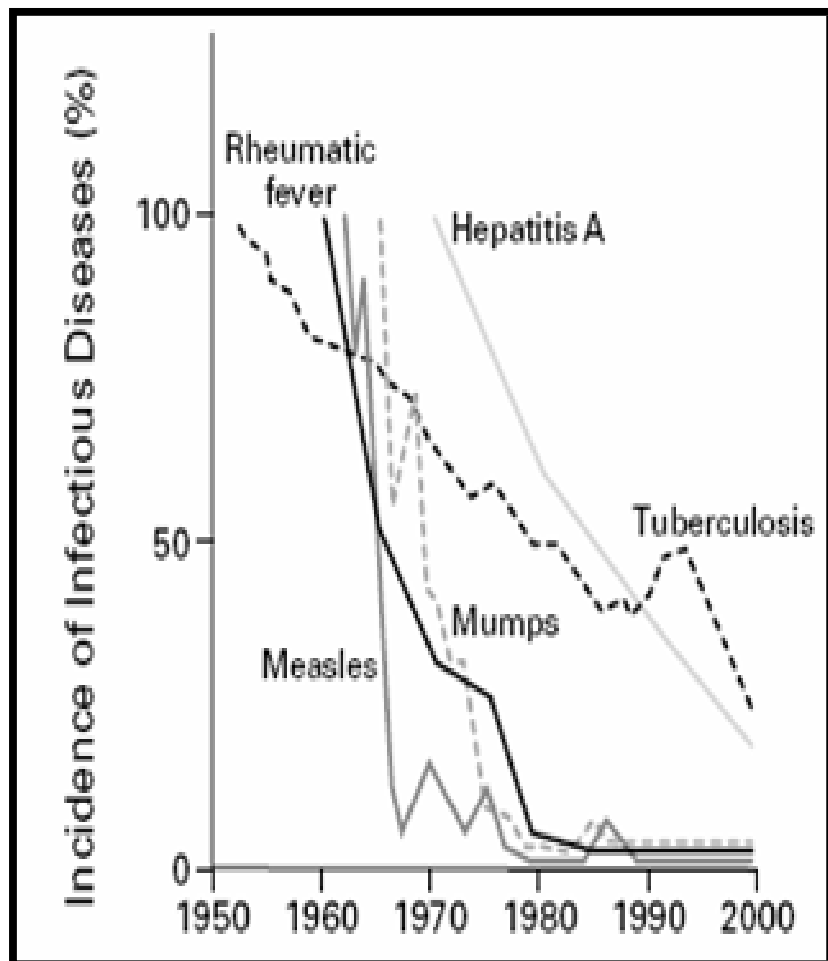
# Environmental Epigenetics



- Effects of vinclozolin (antiandrogenic fungicide) on reproduction were caused by DNA methylation of specific genes
- Effects transferred through male germ line

# Changing Rates of Disease

*United States and Northern Europe*

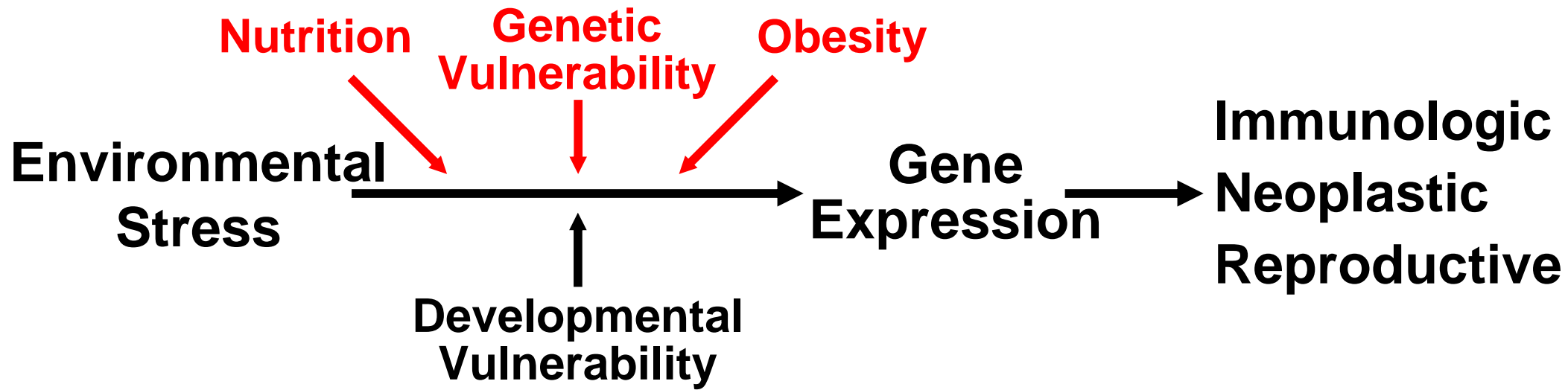


Bach. *NEJM* 2002; 347:911

Vercelli. *J Allergy Clin Imm* 2004; 113:381



# Epigenetic Inheritance and Human Disease

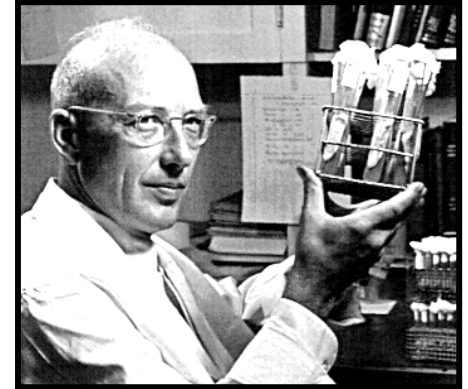
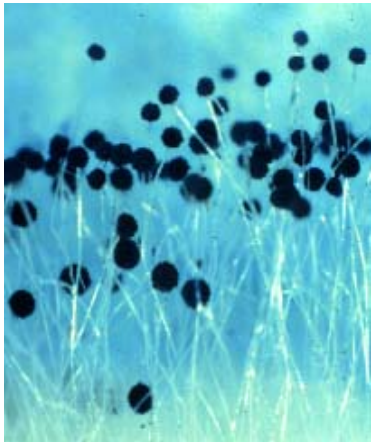


# Environmental Genomics and Human Disease



# Environmental Genomics

*Beadle the first environmental geneticist  
(one gene – one enzyme)*



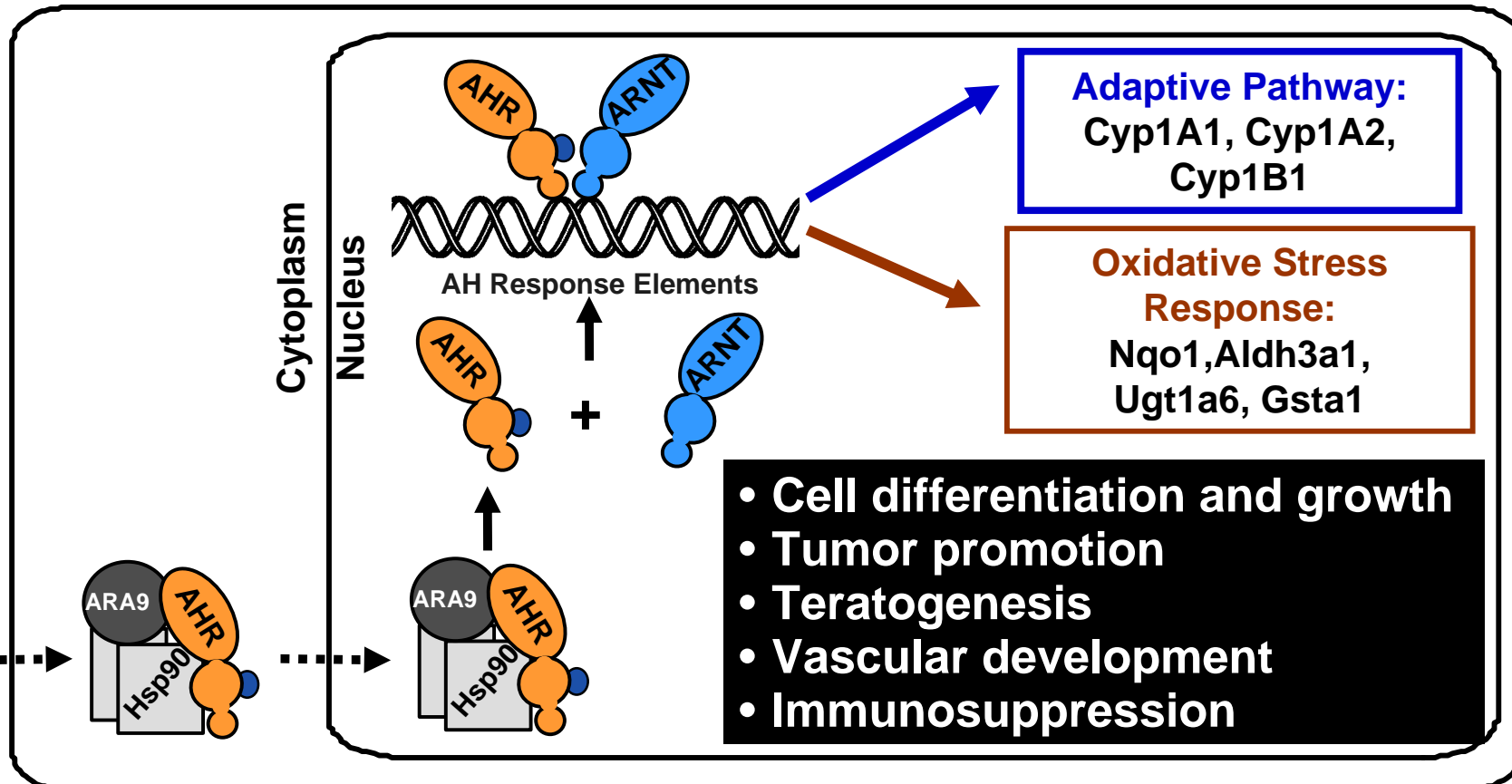
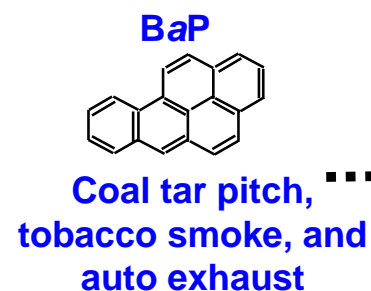
1903-1989



# Aryl Hydrocarbon Receptor (AHR)

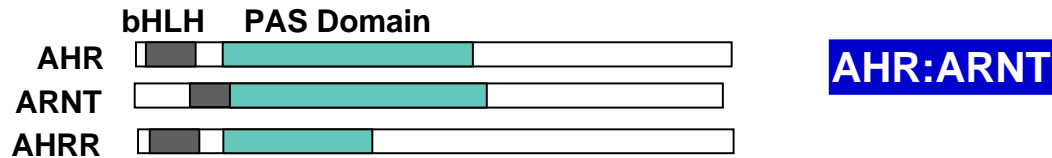
- Discovered due to the carcinogenicity of polycyclic aromatic hydrocarbons
- One of the first receptors to mediate carcinogenesis (1st orphan receptor)
- Evolutionarily conserved (*C. elegans* to humans)

Chris Bradfield  
Dan Nebert

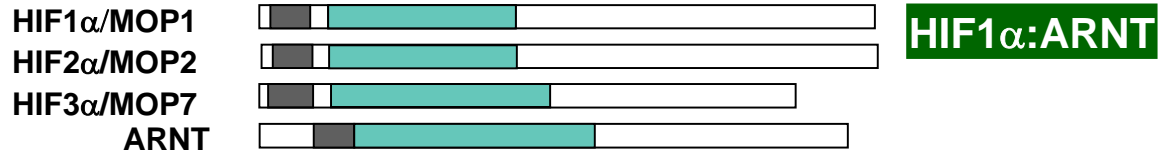


# PAS Superfamily: *Environmental Sensors*

## Dioxin



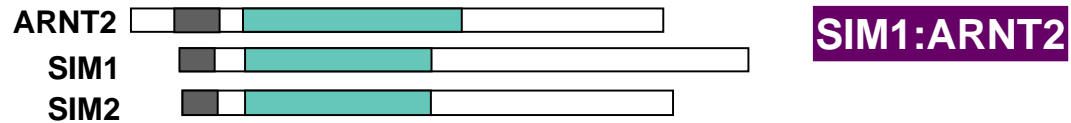
## Hypoxia



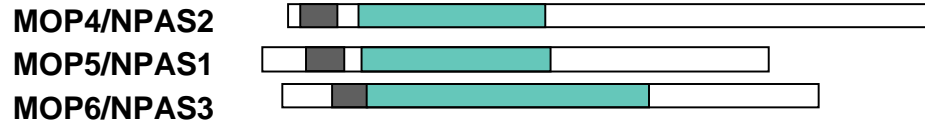
## Circadian



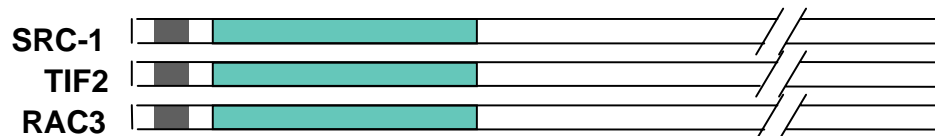
## Neurogenesis



## Orphans

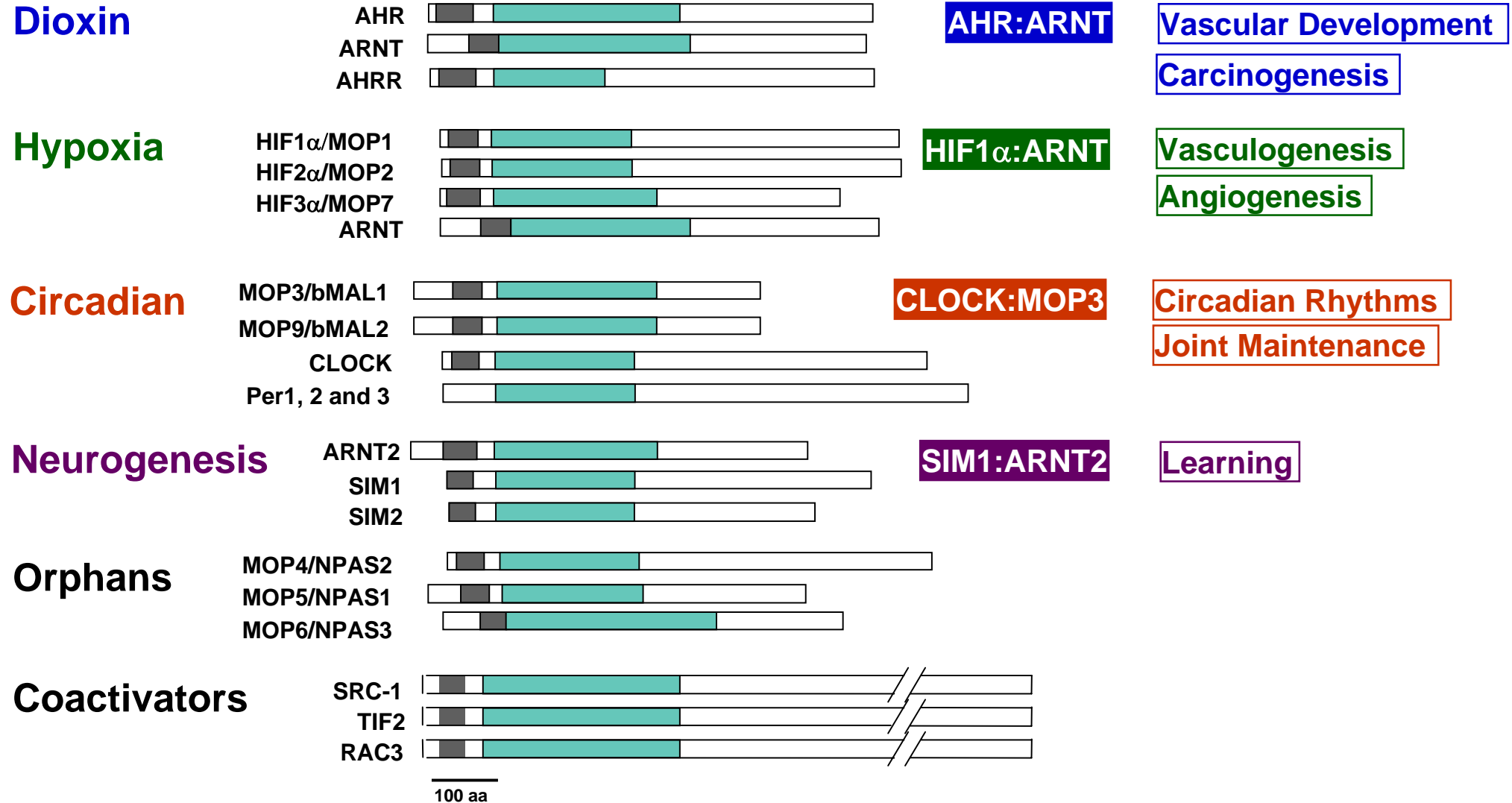


## Coactivators



100 aa

# PAS Superfamily: *Physiologic Sensors*

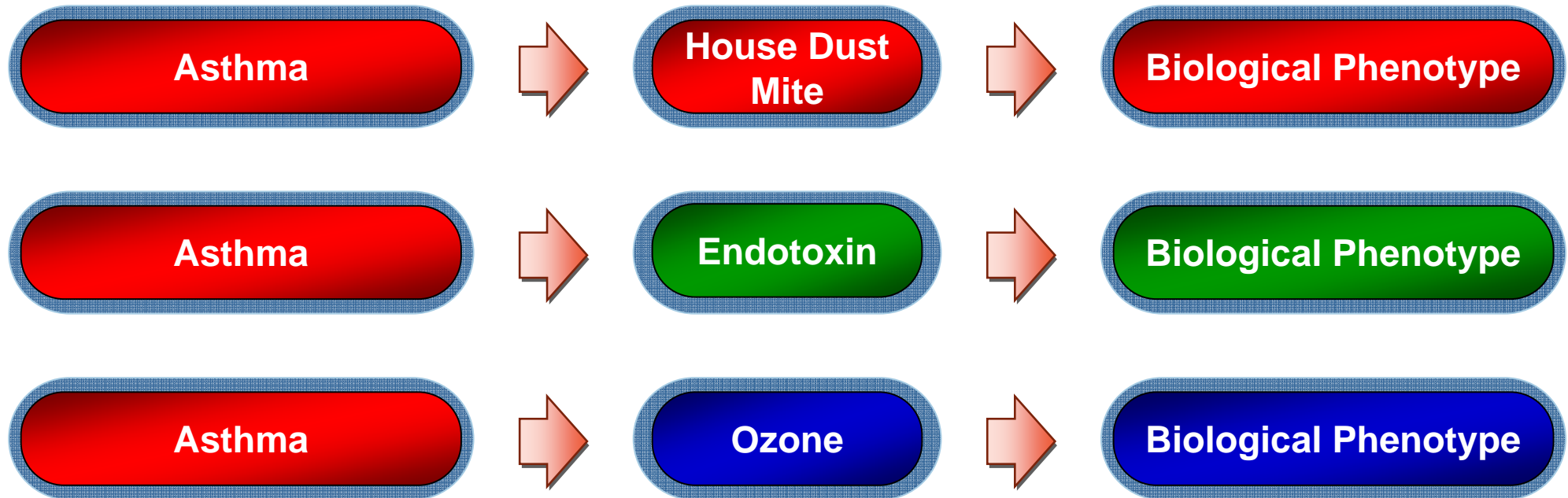




# Exposures Can Simplify Complex Diseases



# Exposures Can Simplify Complex Diseases



**Derivation Stage**

**Atopic  
Asthmatic**

**Atopic  
Nonasthmatic**

**Nonatopic  
Asthmatic**

**Nonatopic  
Nonasthmatic**

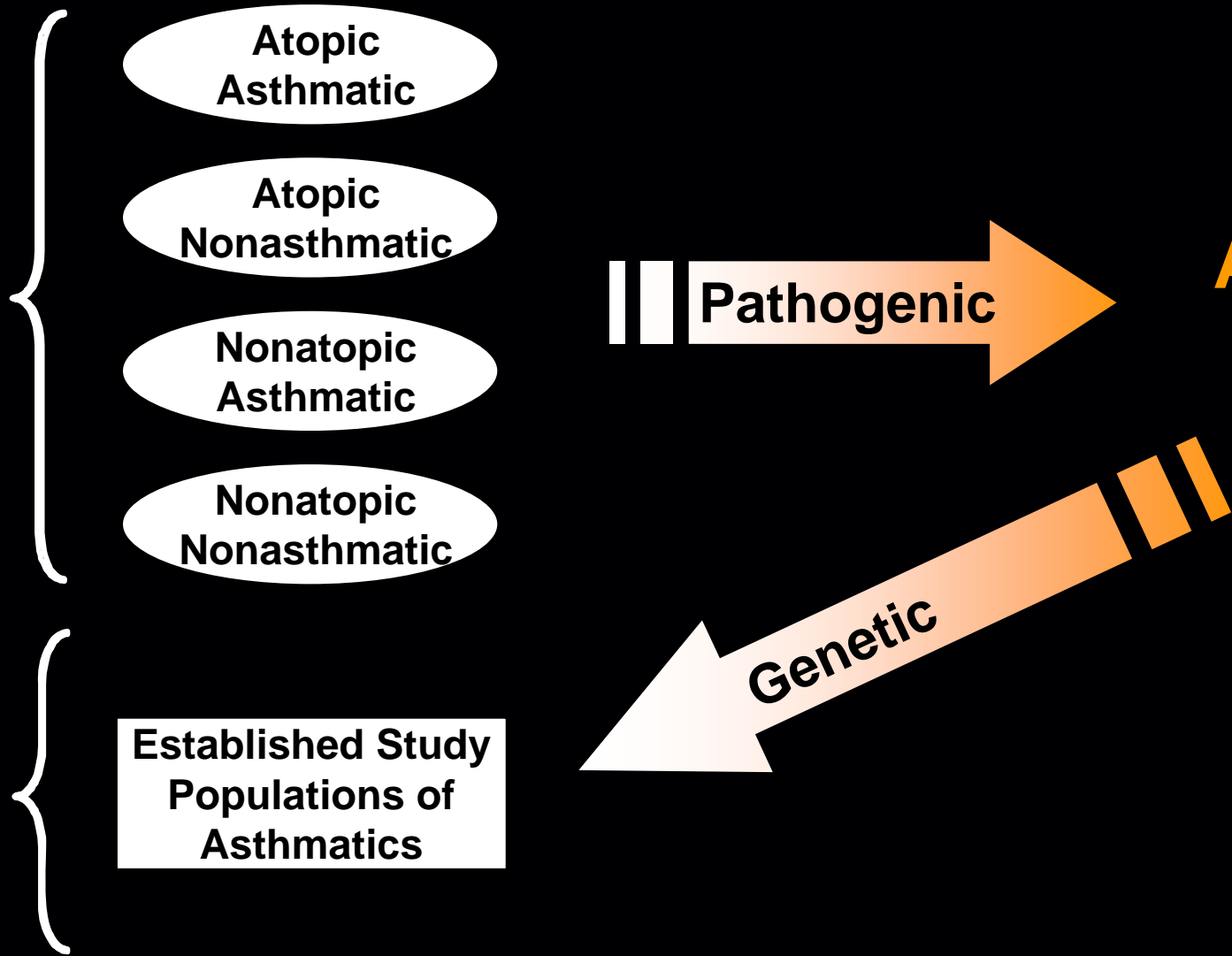
**Test Stage**

**Established Study  
Populations of  
Asthmatics**

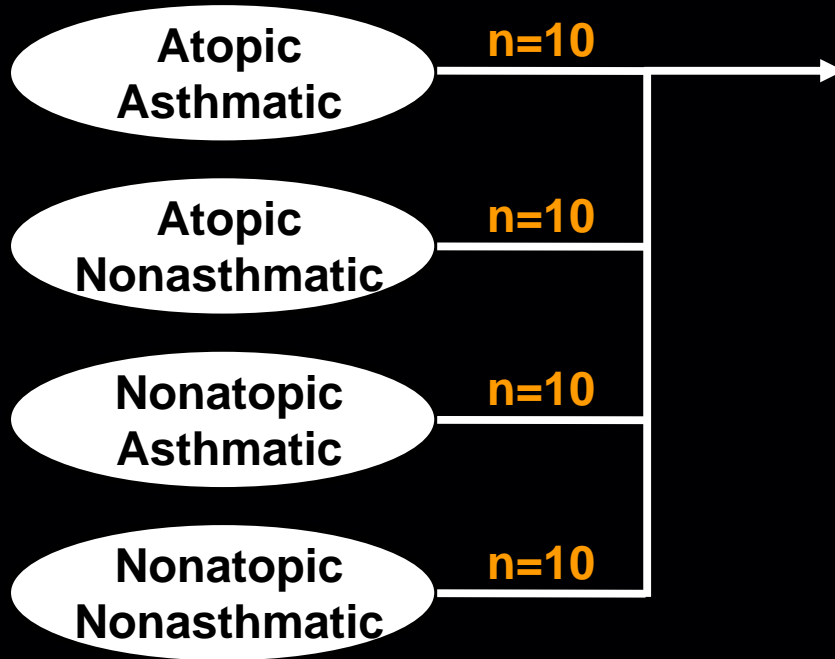
**Pathogenic**

**Genetic**

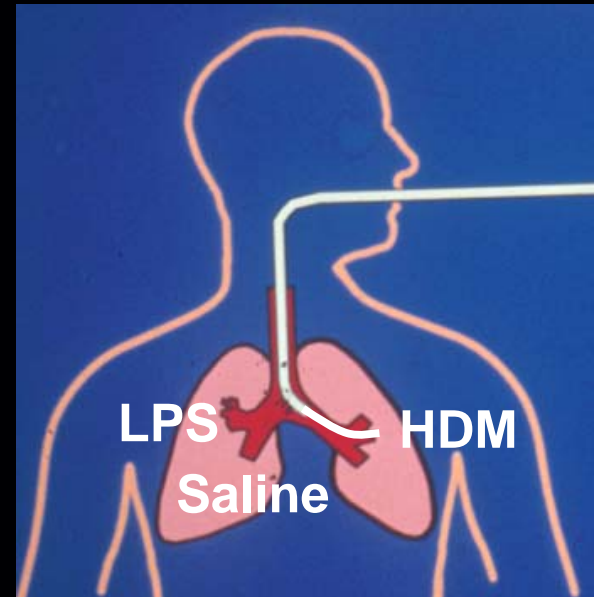
**Asthma  
Genes**



# Derivation Stage



**Airway Challenge (Saline, LPS, and Dust Mite), BAL, and Brush Biopsy**

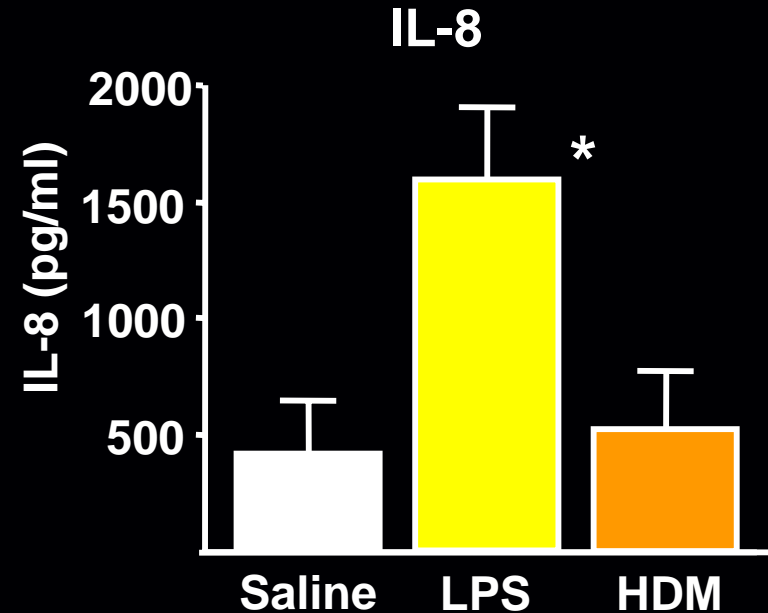
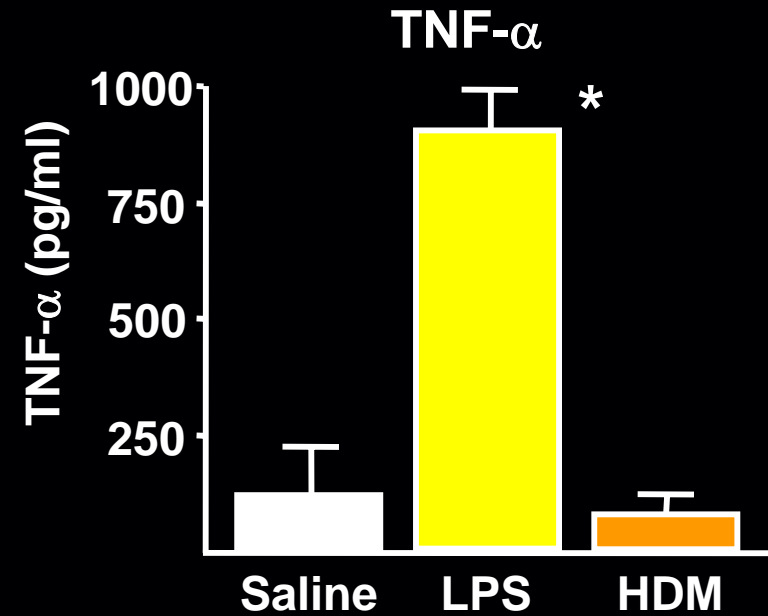
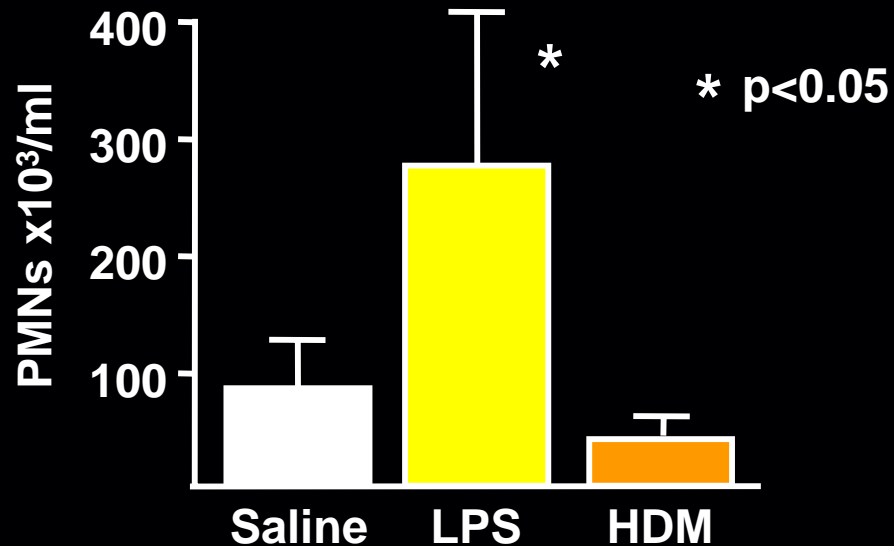


John Sundry  
John Quackenbush  
Ivana Yang  
John Tomfohr  
Cathy Foss

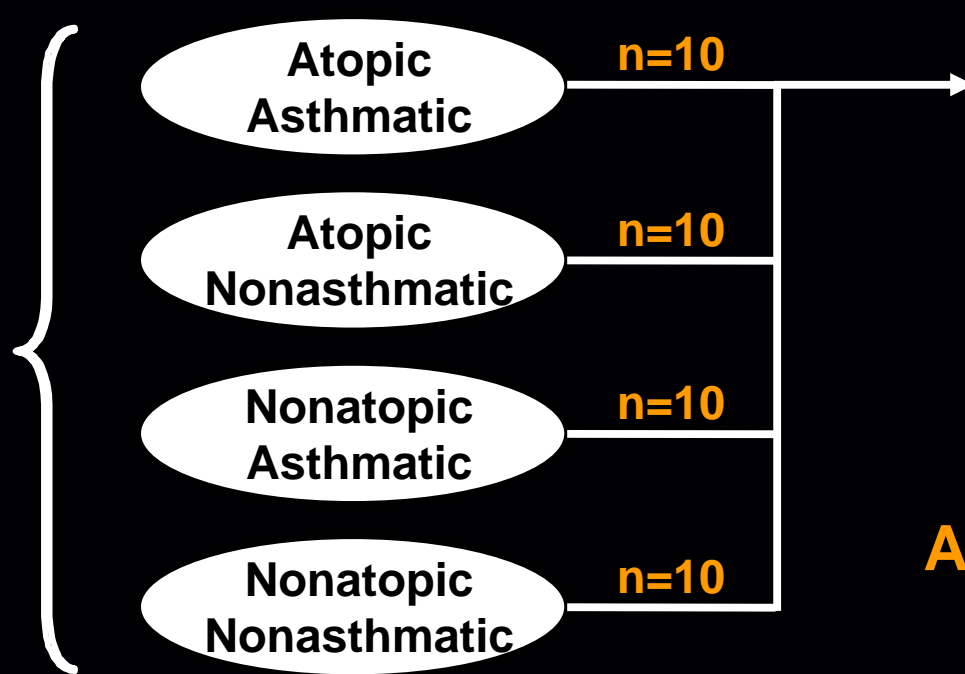
# Biological Response to Environmental Toxins

[15 nonatopic/nonasthmatics]

Lavage Cellularity - PMNs



# Derivation Stage



Airway Challenge (Saline, LPS, and Dust Mite), BAL, and Brush Biopsy



Differential Expression of Genes/ESTs by Microarray Analysis

**Atopic/Asthmatics (n=10)**

**VS**

**Nonatopic/Nonasthmatics (n=10)**

John Sundy

Cathy Foss

Jaspal Singh

John Tomfohr

Ivana Yang

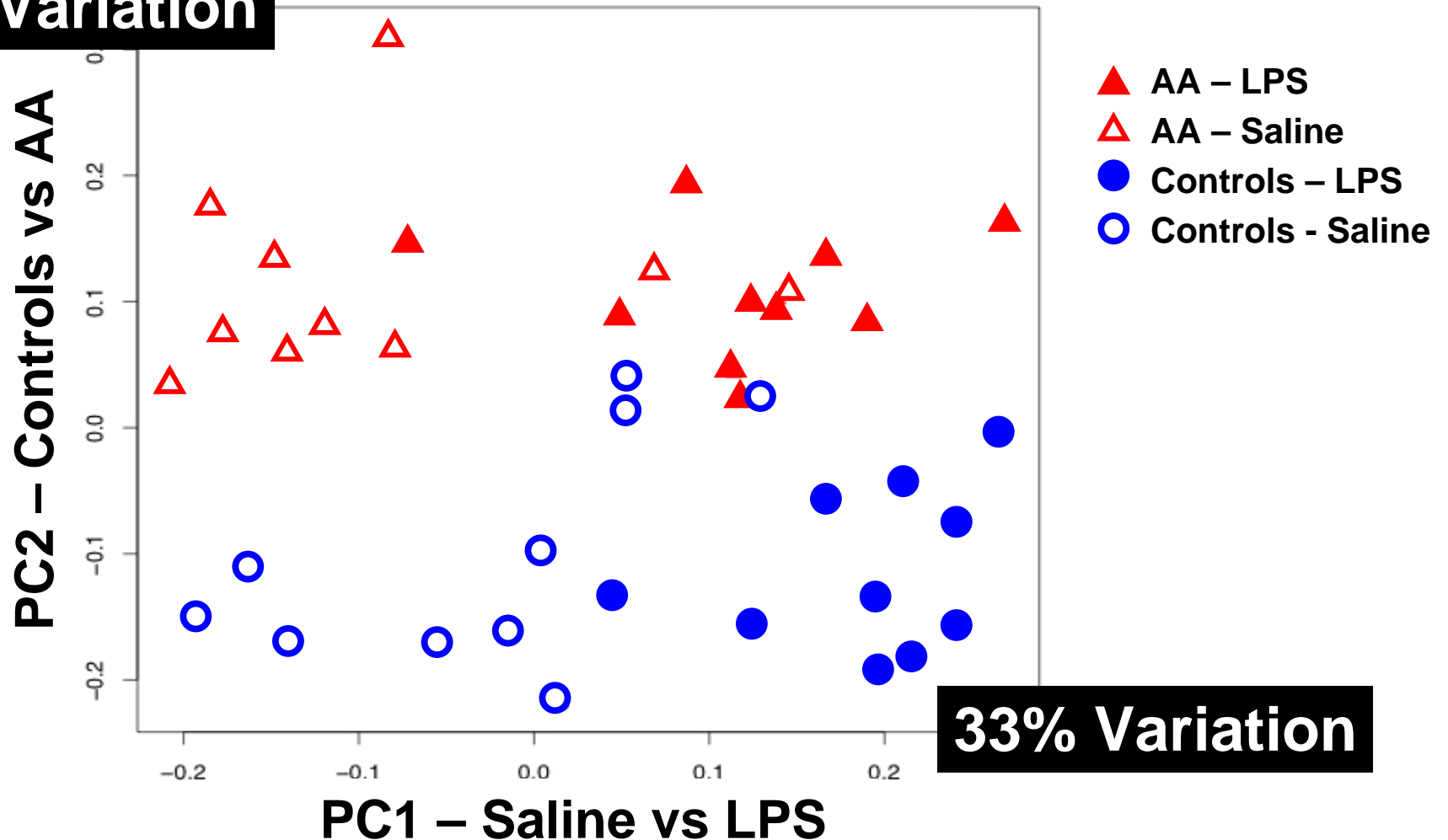
John Quackenbush



# Atopic Asthmatics and Controls are Distinct but Equally Responsive to LPS

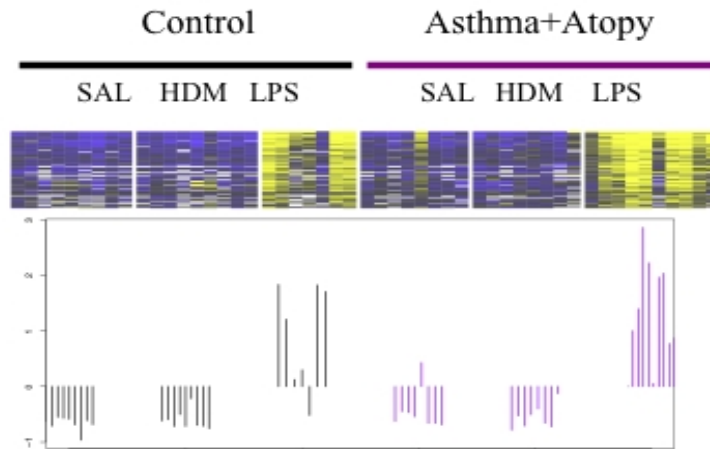
[Principal Component Analysis – 1000 genes]

13% Variation



# Genes Involved in the Response to LPS

## [k-means clustering]



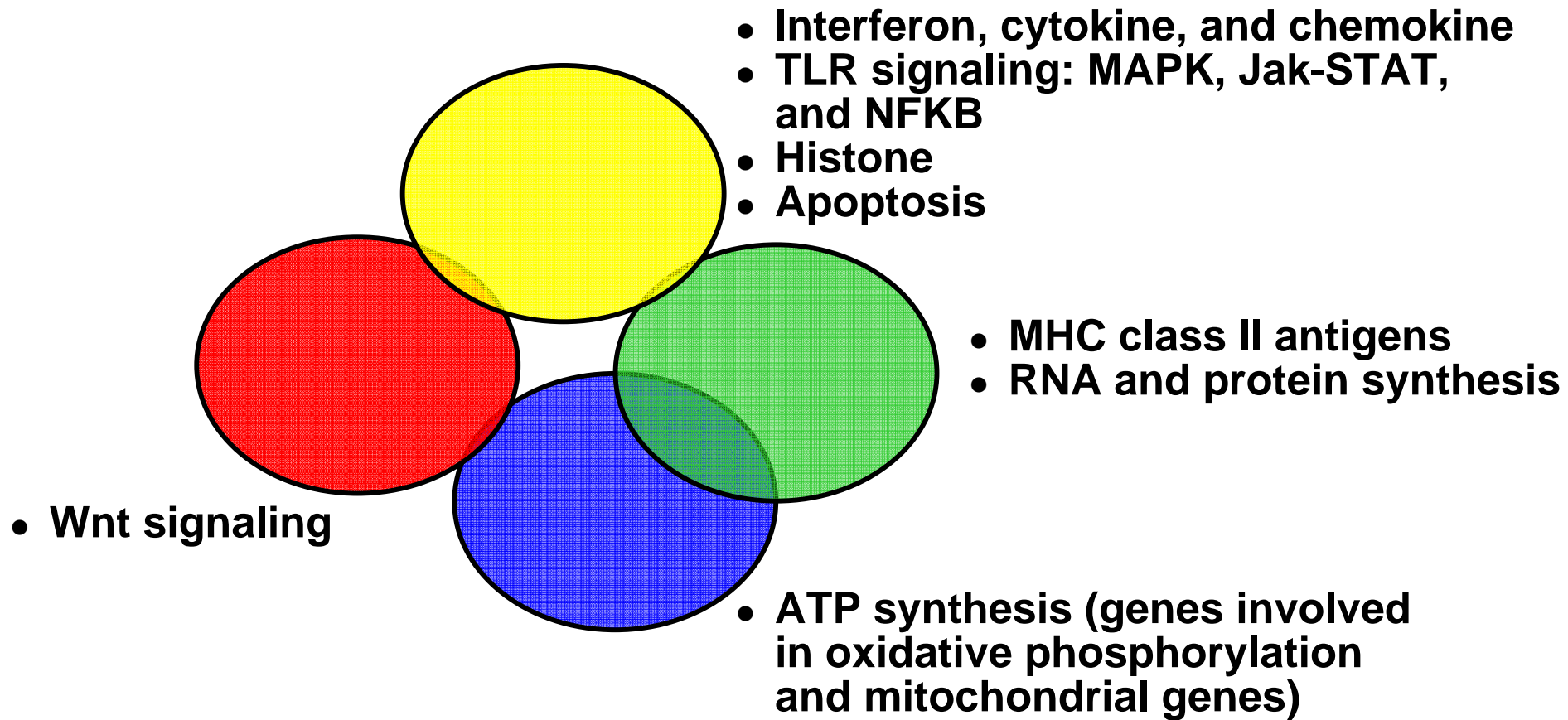
NT5C3	INDO	DDX58	<b>IFIT5</b>	<b>IRF7</b>
USP18	HERC5	<b>IFIT3</b>	KIAA1404	PLEKHA4
PNPT1	<b>IFIH1</b>	<b>G1P2</b>	GNB4	<b>IFRG28</b>
NEXN	BG547557	SAMD9L	DUSP5	TOR1B
SLC25A28	NCOA7	TCF4	TCTEL1	MGC20410
CXCL11	GTF2B	<b>IFIT1</b>	<b>IFI44</b>	<b>MX1</b>
PML	DTX3L	XRN1	RSAD2	LGP2
SAMD9	GBP4	IL15RA	LMO2	SP110
RGL1	TNFSF10	RIN2	HERC6	IL10RA
ATF3	TDRD7	SLAMF7	FLJ11286	WARS

**Interferon**

# Genes Involved in the Response to LPS

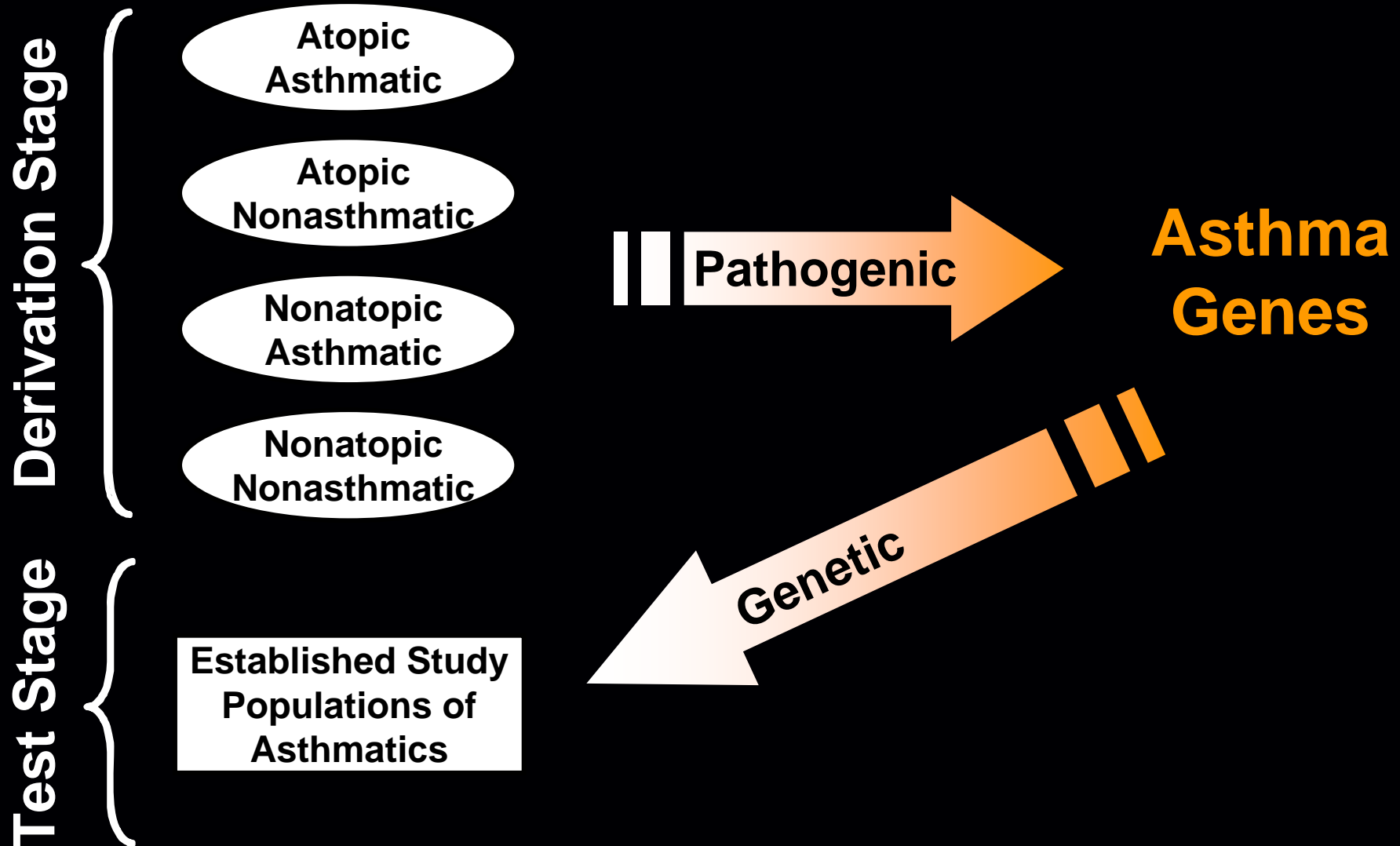
[atopic/asthmatics vs controls]

up ——— LPS ——— down



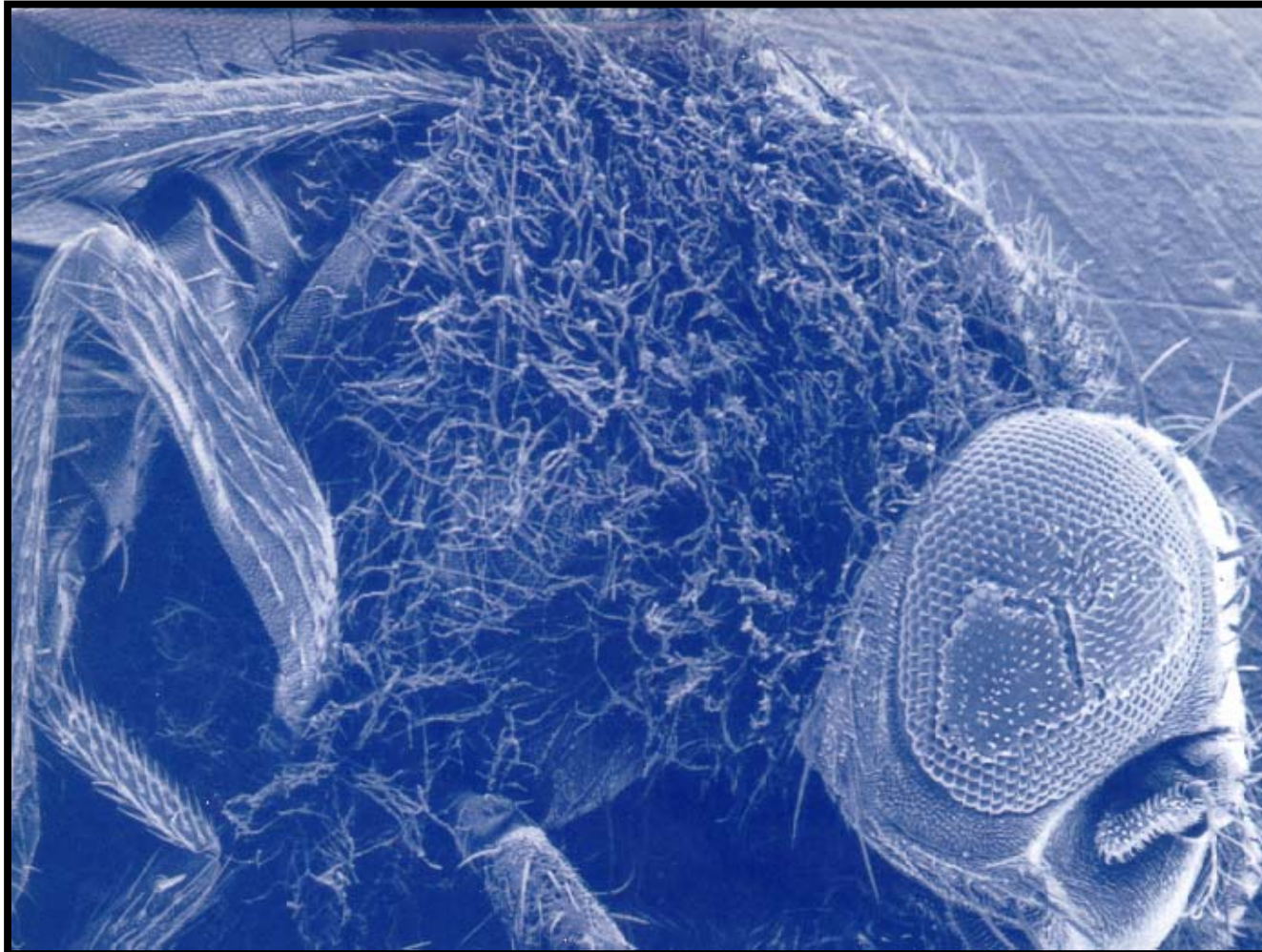
down ——— Atopic/Asthmatic ——— up

# Environmental Genomics and Asthma



# Comparative Genomics

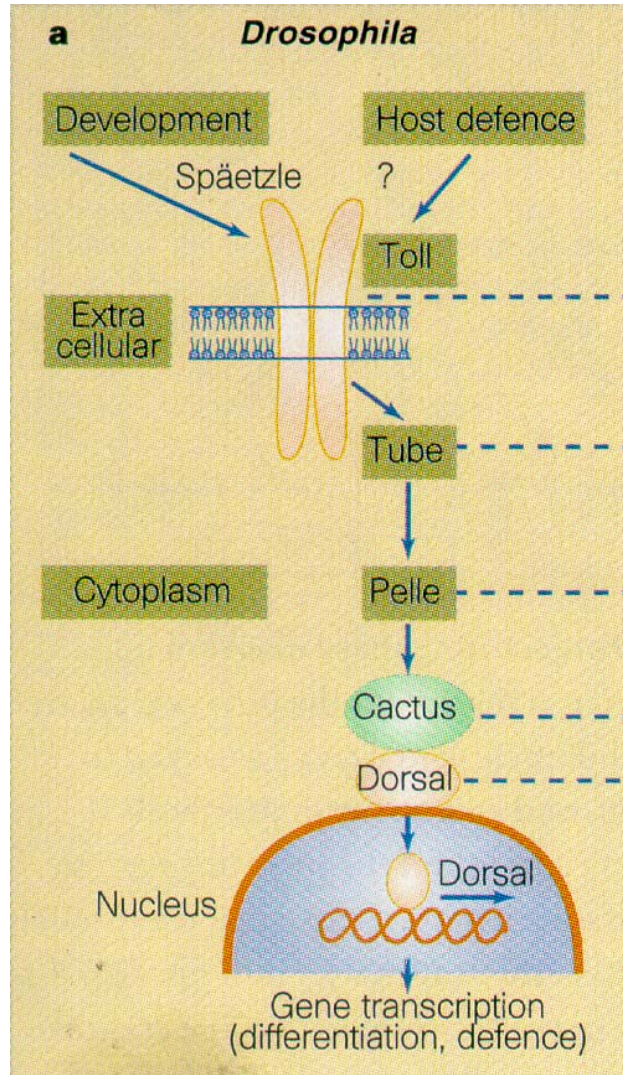
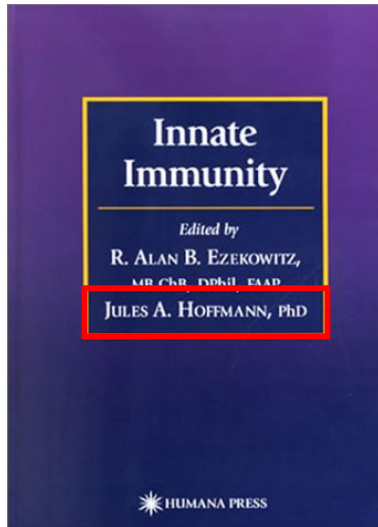
*Evolutionary Conservation of Biology*





# Comparative Genomics

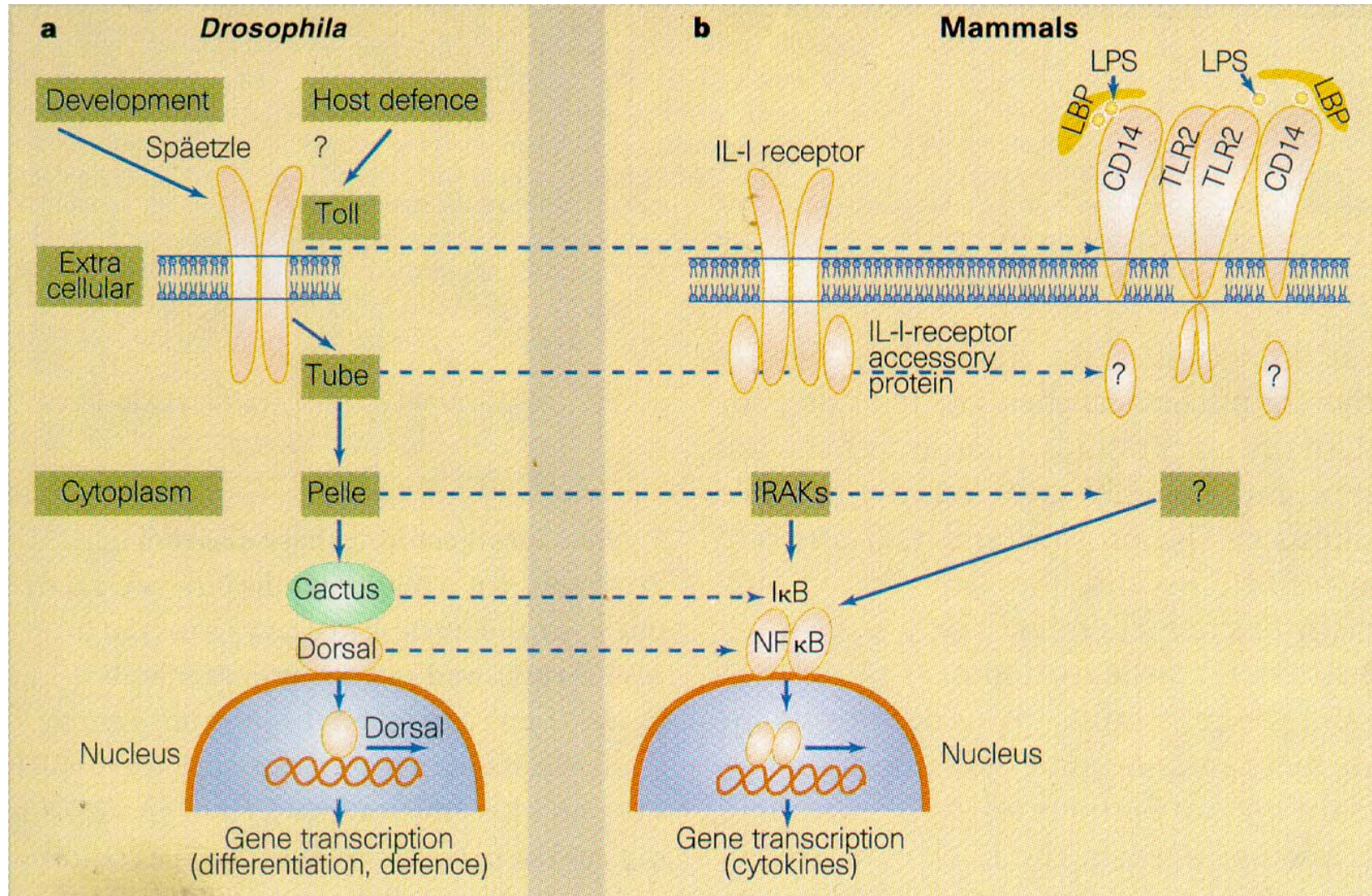
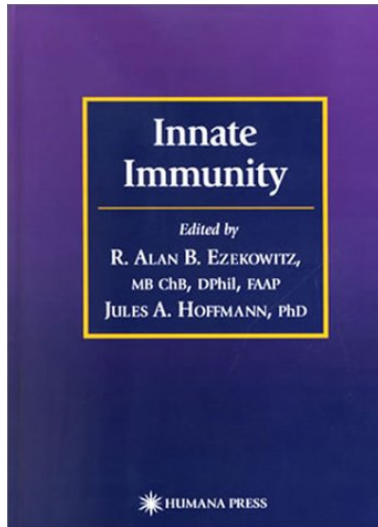
## *Evolutionary Conservation of Biology*





# Comparative Genomics

## *Evolutionary Conservation of Biology*





# nature genetics

Volume 25  
June, 2000



## Polymorphisms in *TLR4* blunt the response to LPS in humans

Brian Schutte et al.



The  
New England  
Journal of Medicine

Volume 347

July 18, 2002

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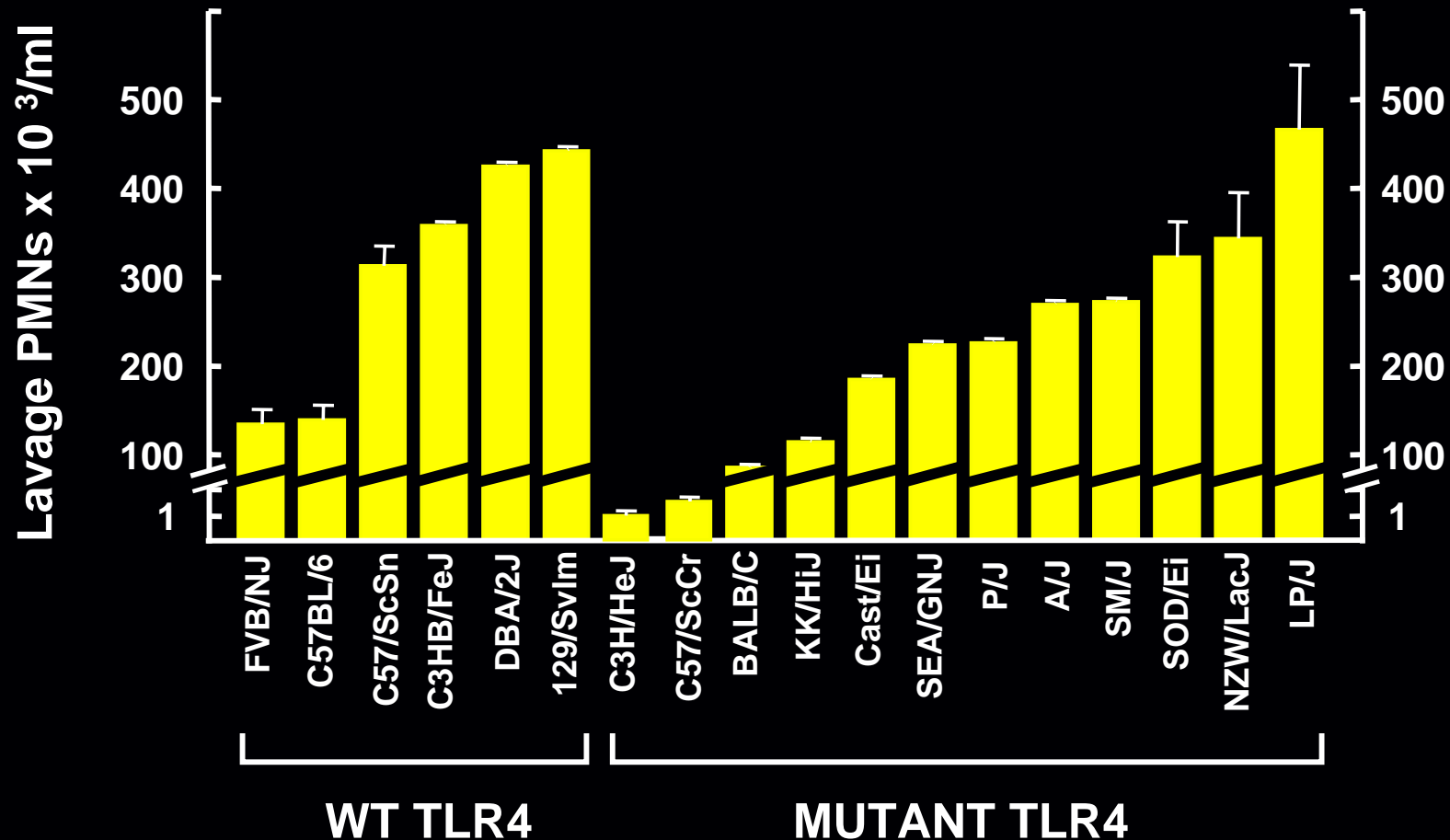
### CLINICAL IMPLICATIONS OF BASIC RESEARCH

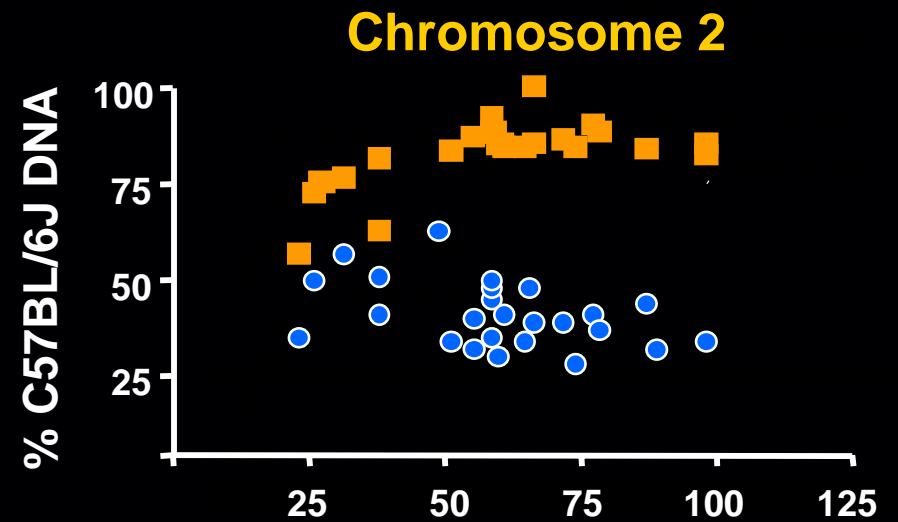
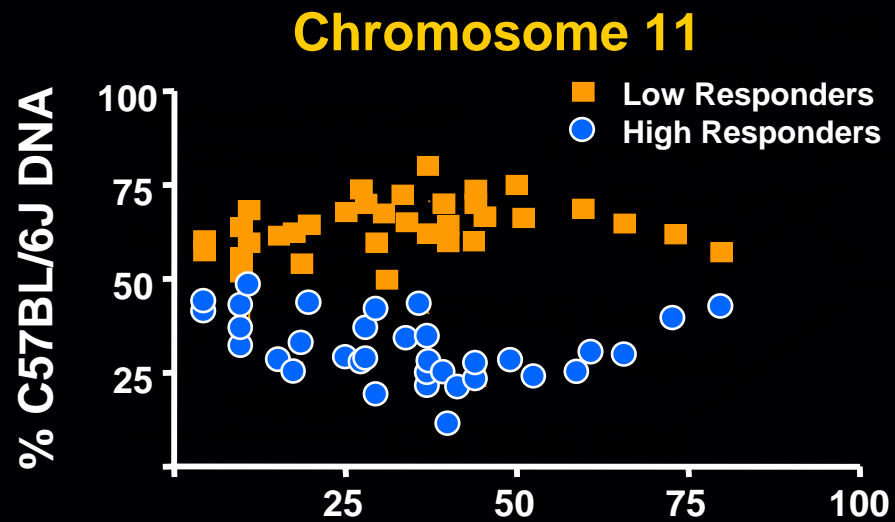
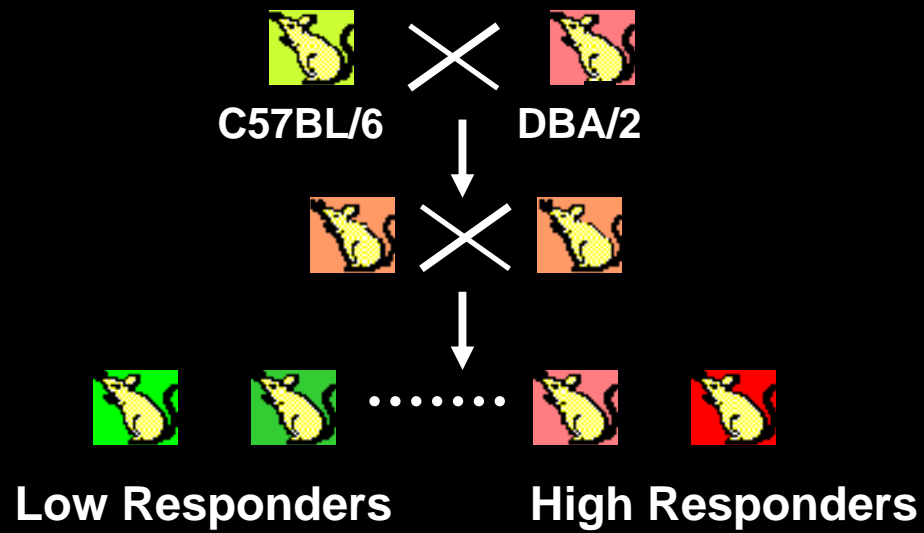
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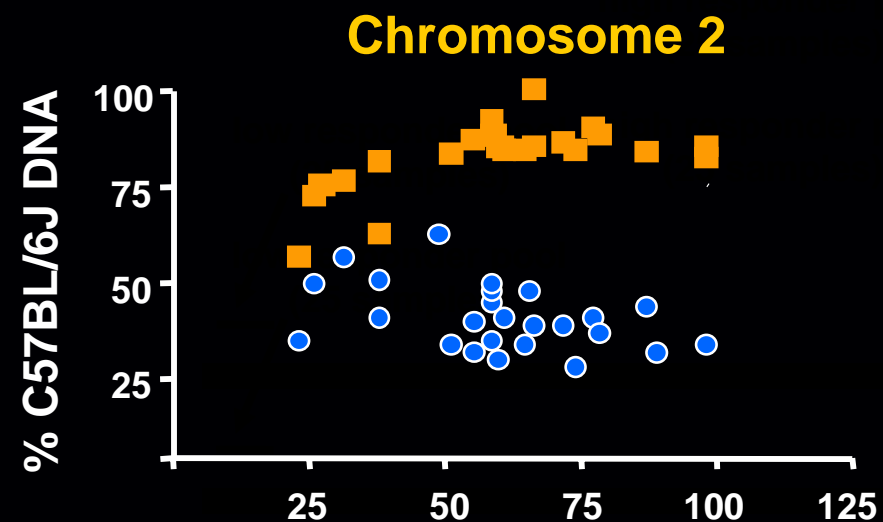
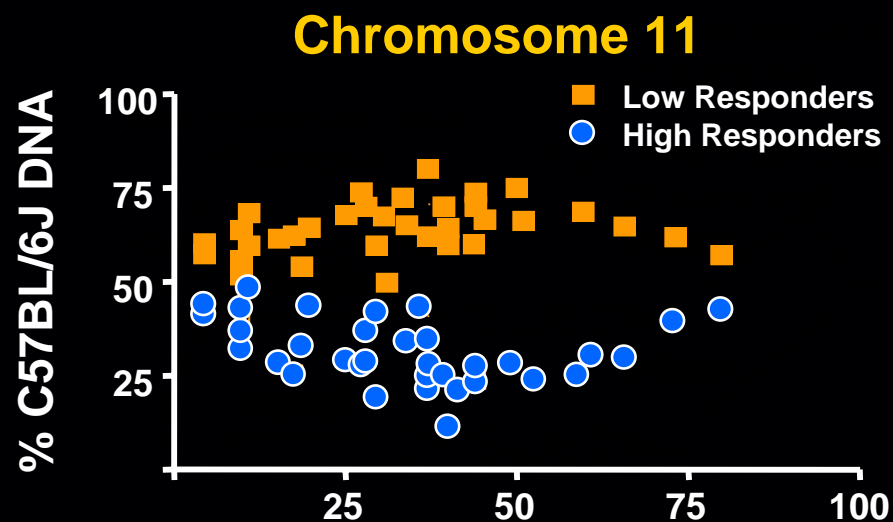
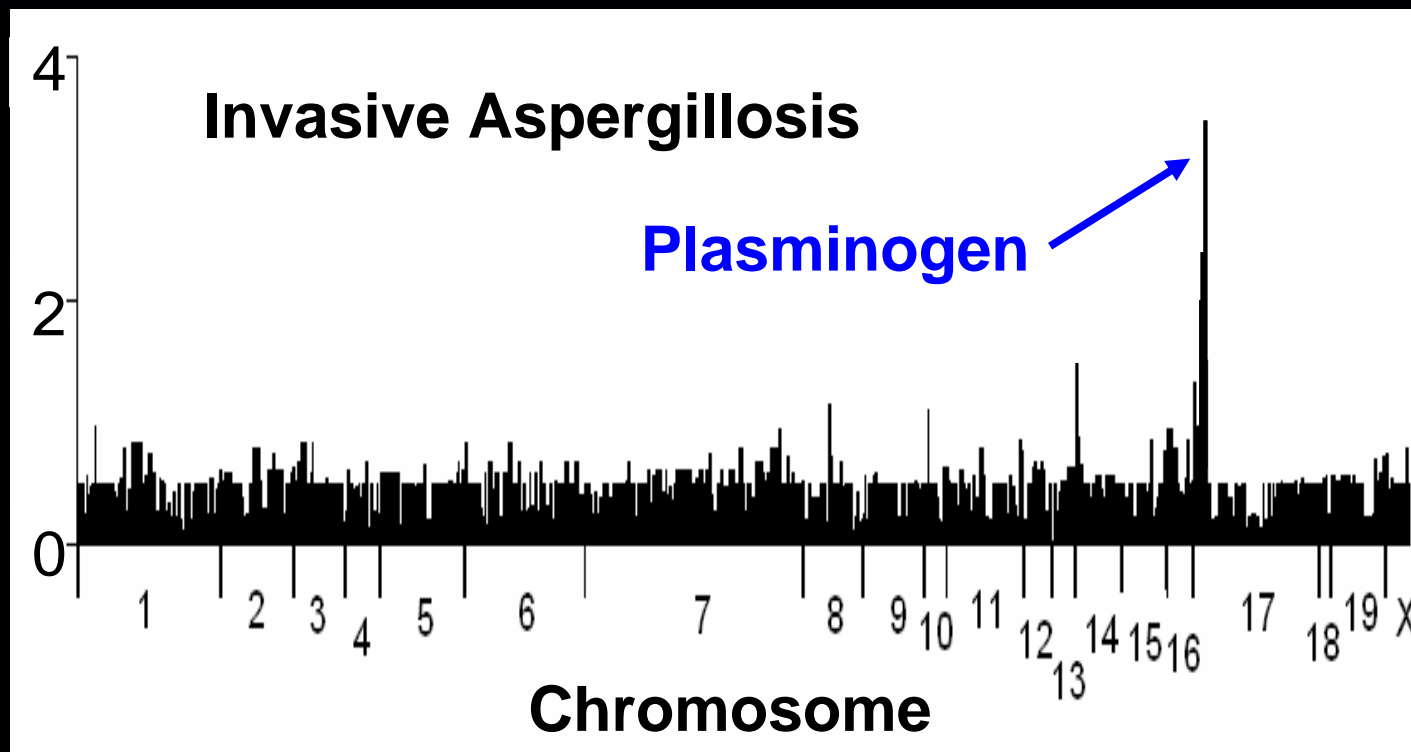
## Polymorphisms in *TLR4* protect humans from atherosclerosis

Steven Kiechl et al.

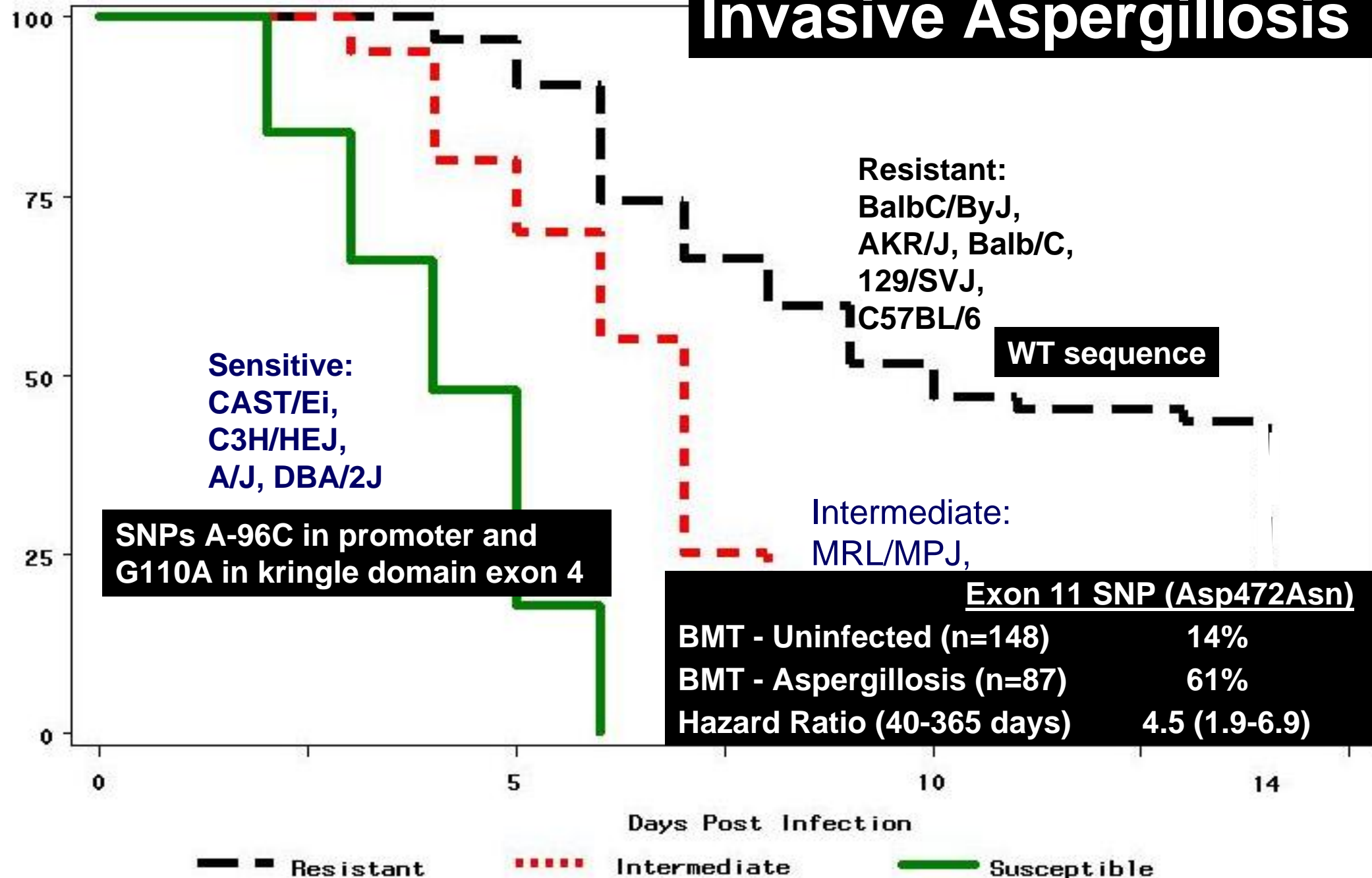
# LPS Responsiveness in Inbred Strains of Mice



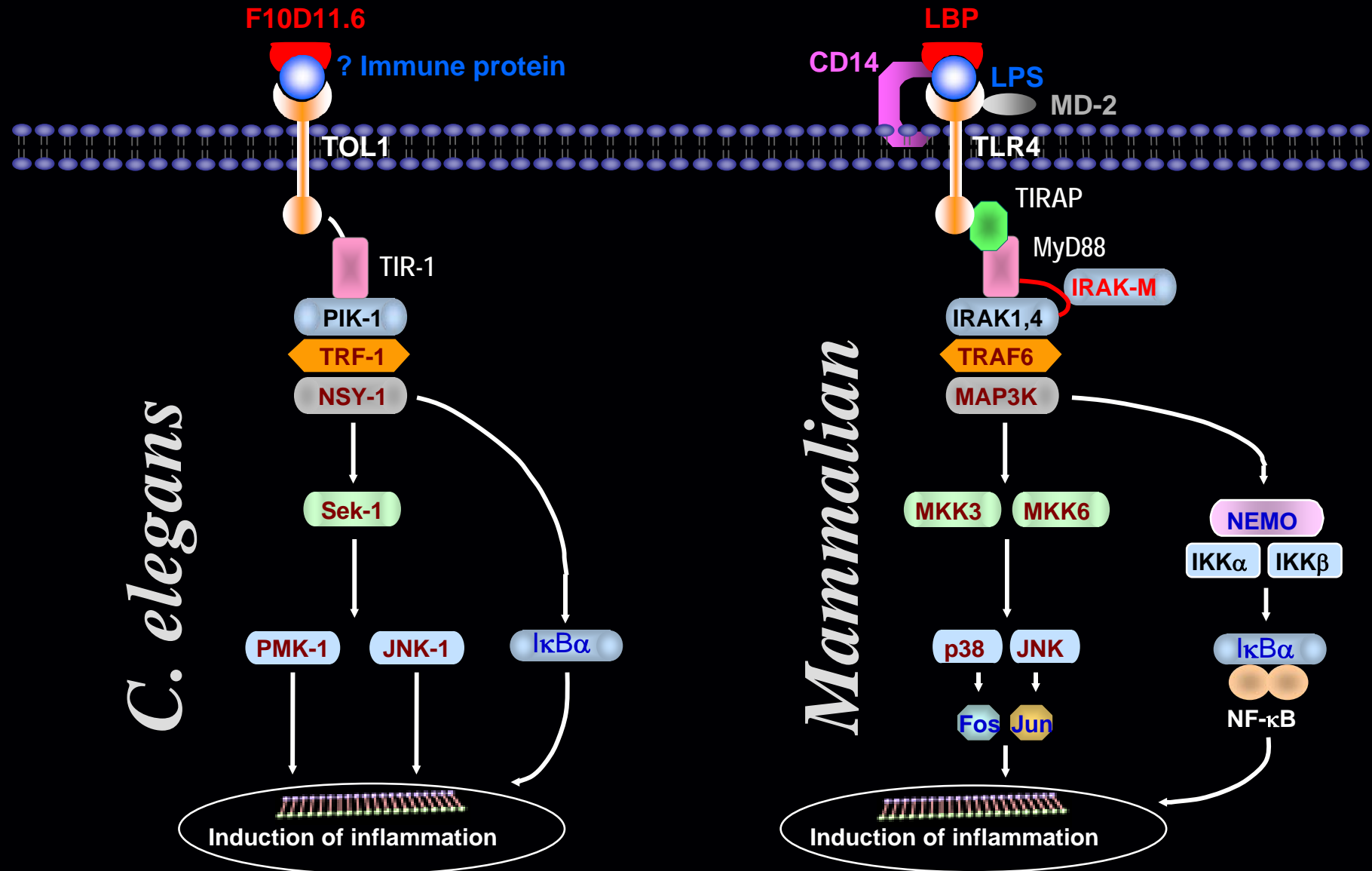




# Invasive Aspergillosis



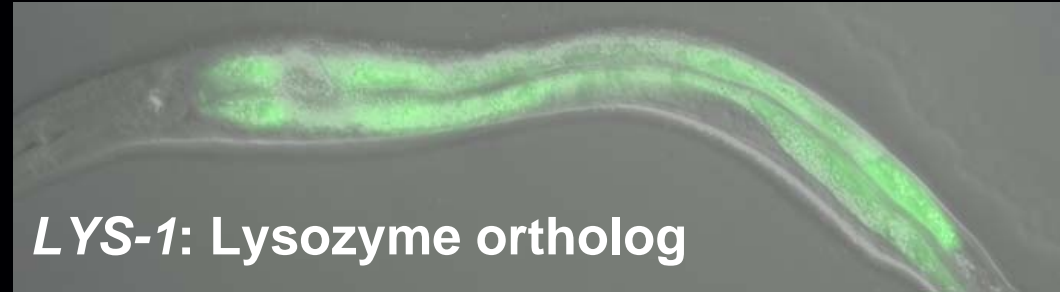
# Comparative Genomics in Innate Immunity



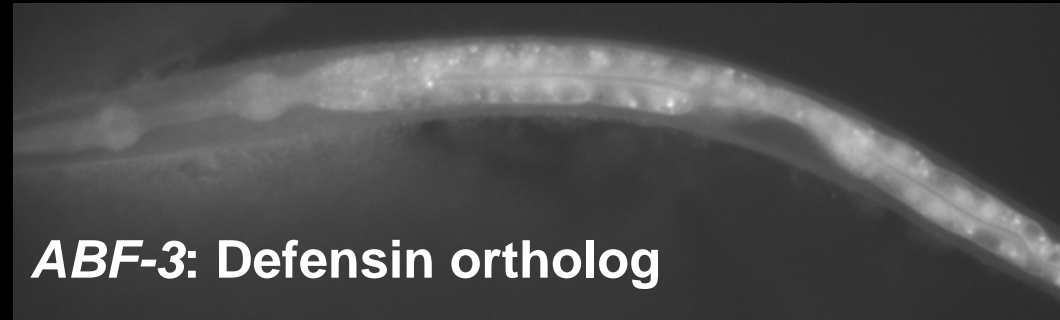
# Approach to Discovery of Innate Genes in *C. elegans*



Label  
promoter of  
antibiotic  
response  
genes with  
GFP



*LYS-1*: Lysozyme ortholog



*ABF-3*: Defensin ortholog

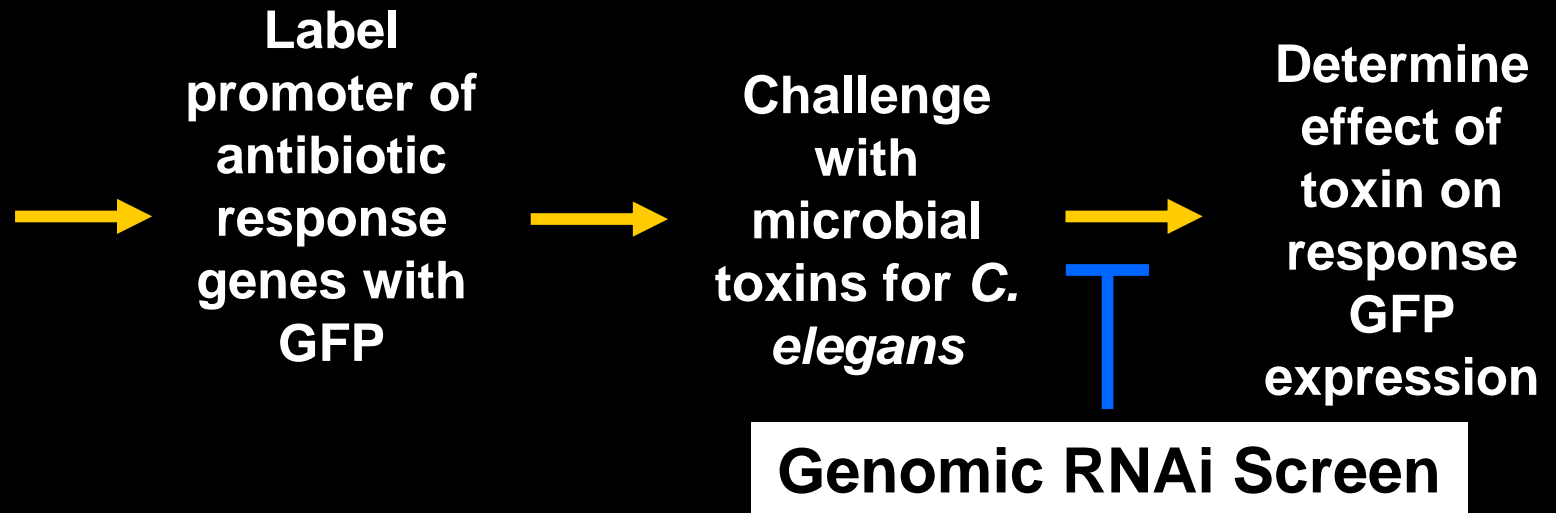


*SPP-7*: Granulysin ortholog

Scott Alper  
Jonathan Freedman

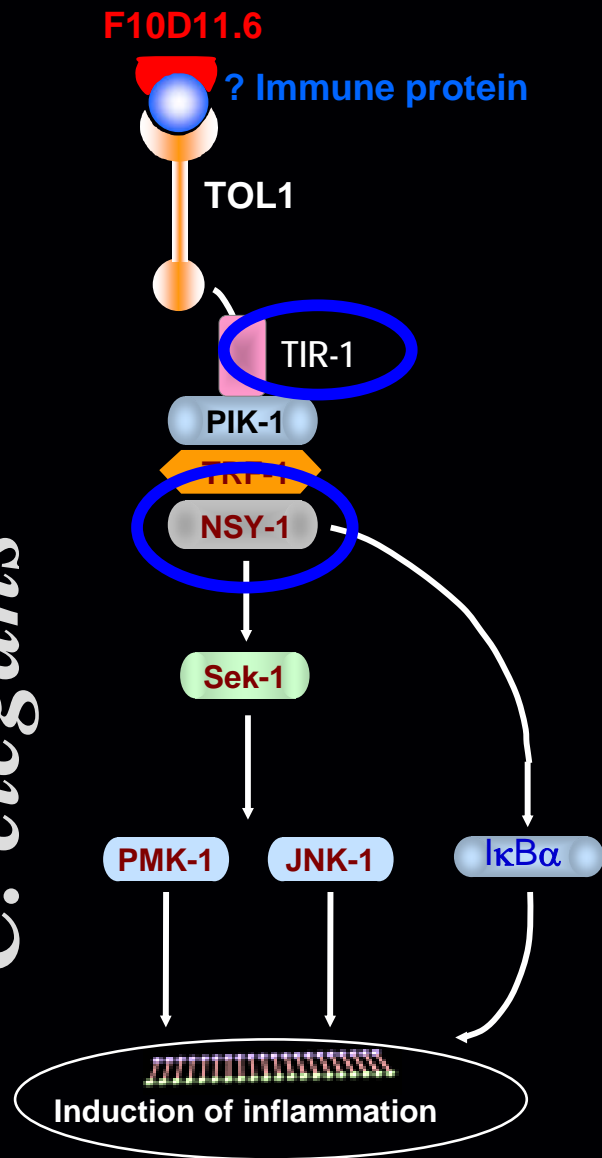


# Approach to Discovery of Innate Genes in *C. elegans*

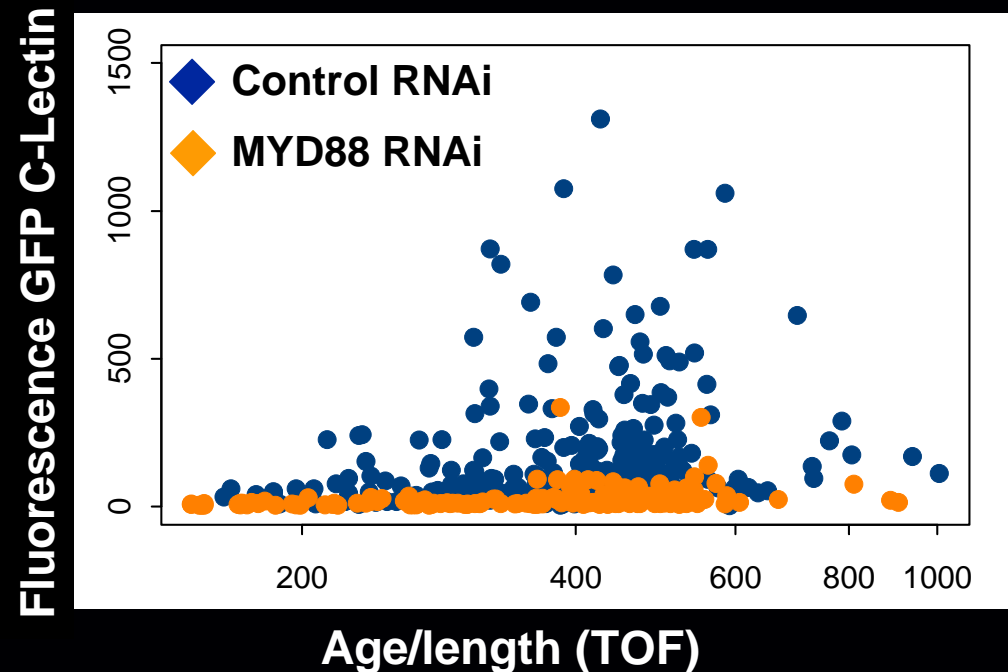
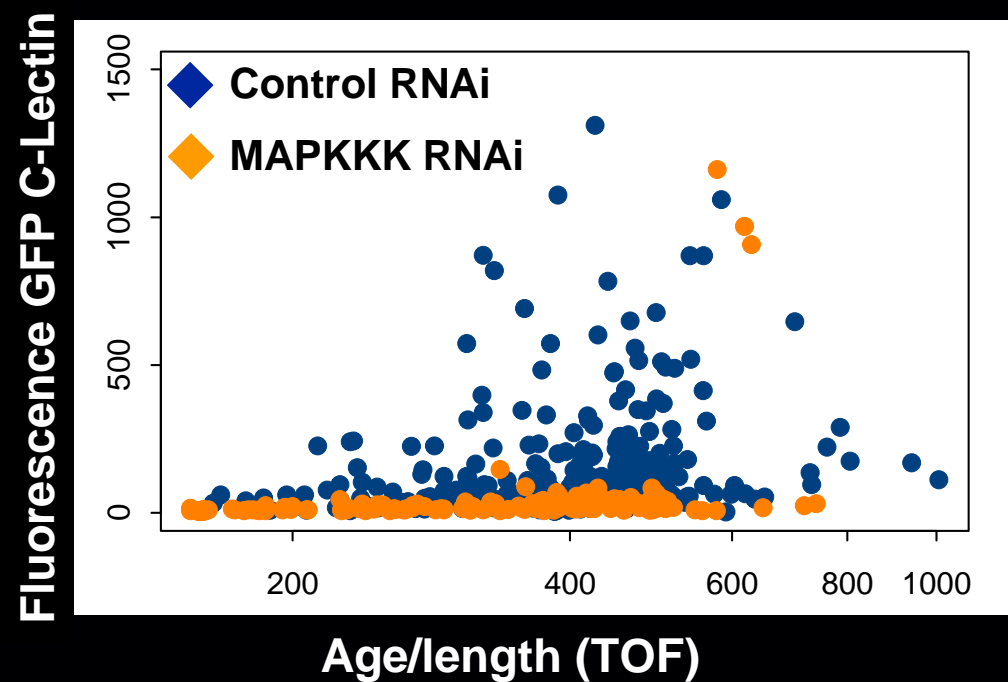


Scott Alper  
Jonathan Freedman

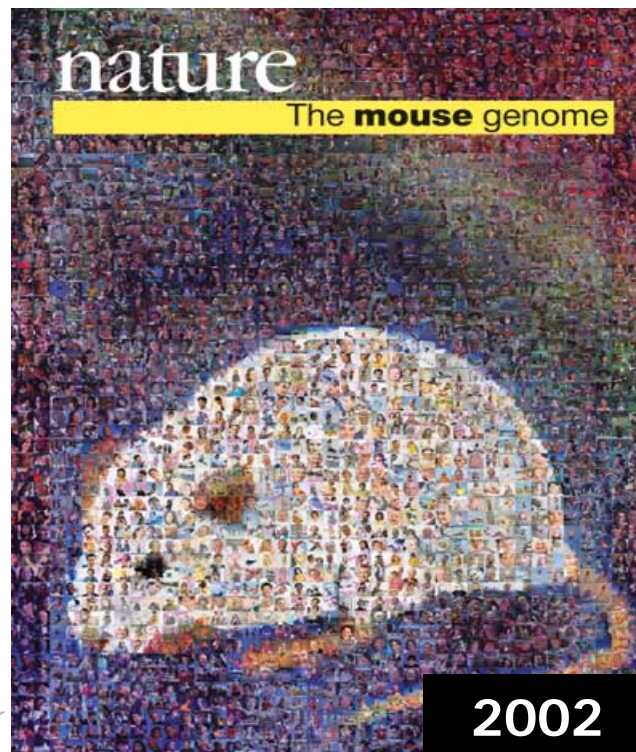
*C. elegans*



Scott Alper  
Jonathan Freedman



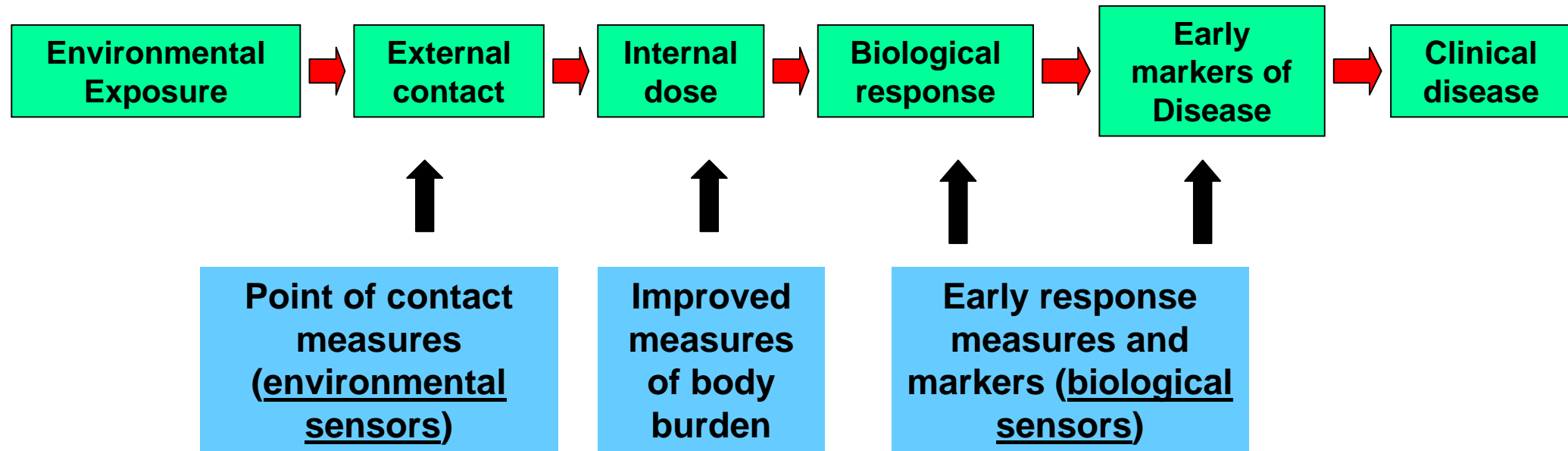
# Why Don't We Know More?



***Genes are only a small part of our make-up...  
the environment has a spectacular impact***

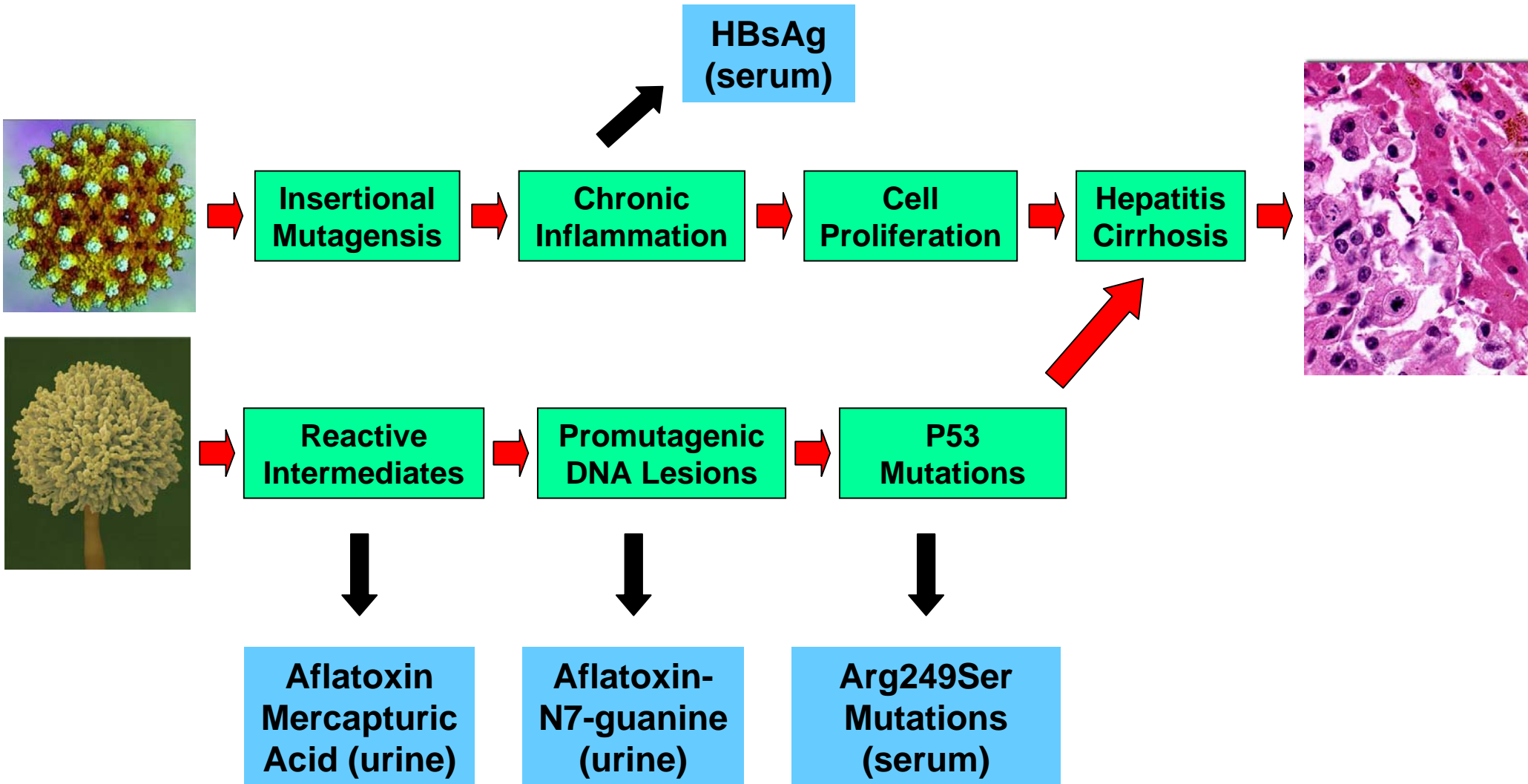
**Eric Lander**

# Infrastructure Needs: More Precise Markers of Exposure



**Links personal exposures to biological response**

# Etiology of Hepatocellular Carcinoma

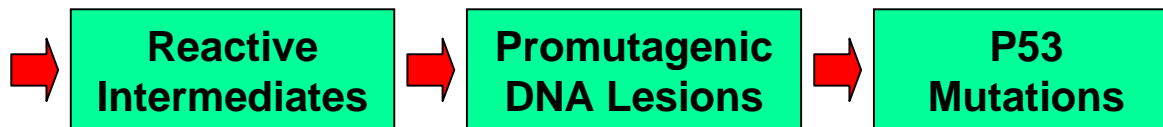
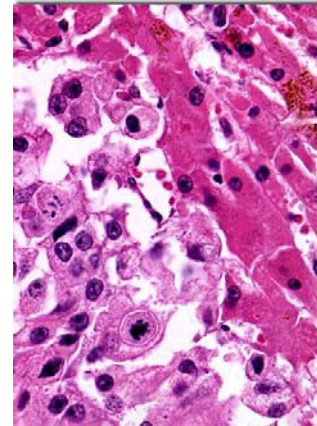
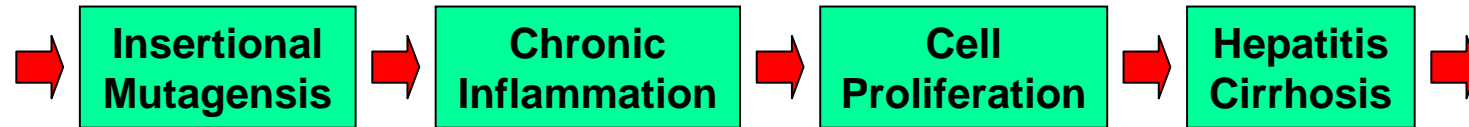
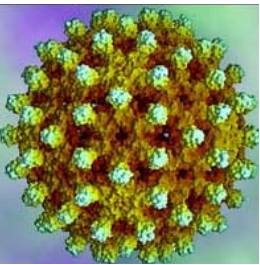




# Etiology of Hepatocellular Carcinoma

No association between dietary aflatoxin and liver cancer

HBsAg  
(serum)



Aflatoxin  
Mercapturic  
Acid (urine)

Aflatoxin-  
N7-guanine  
(urine)

Arg249Ser  
Mutations  
(serum)

	<u>RR</u>
Aflatoxin	3.8
HBV	7.3
Aflatoxin + HBV	60.0

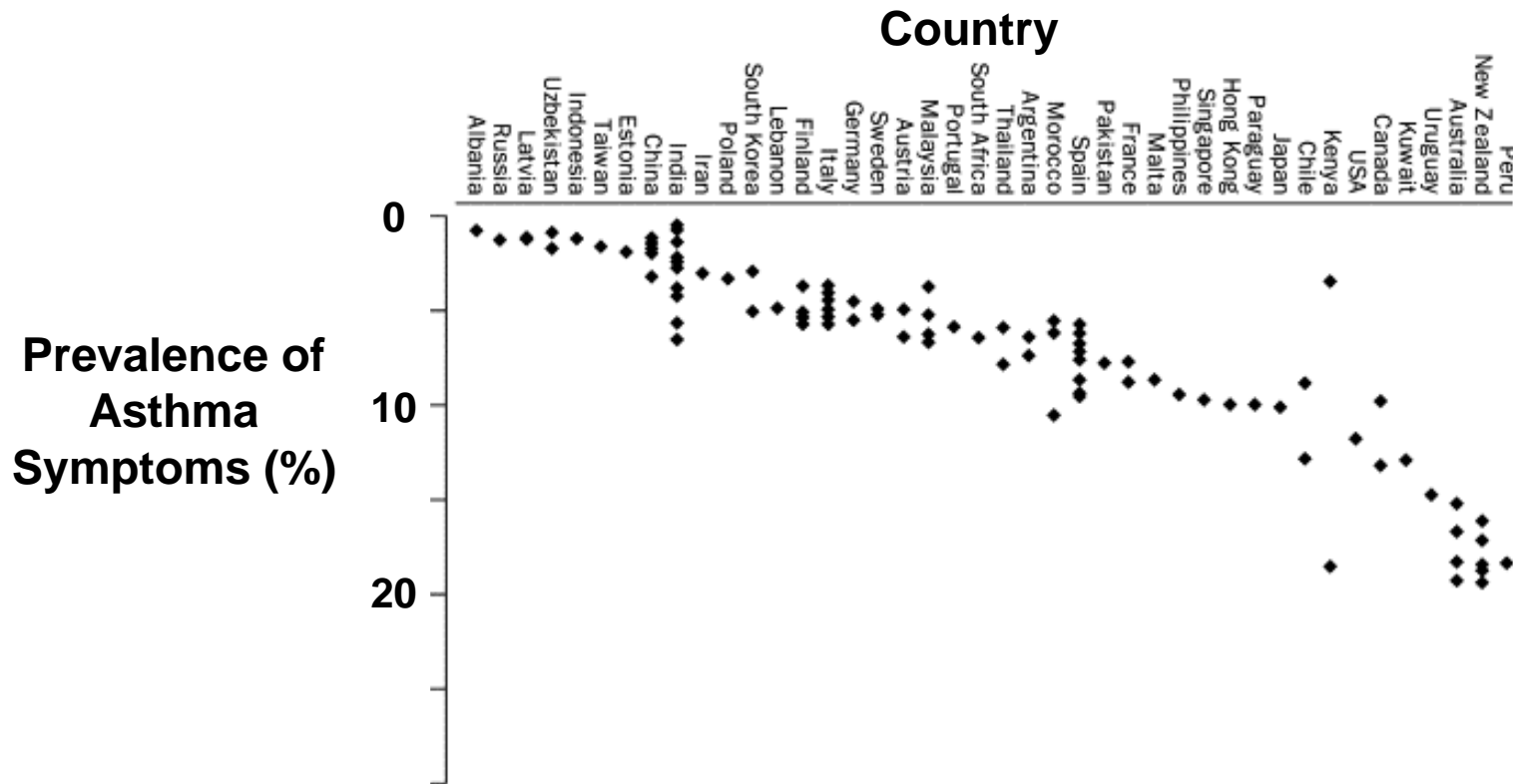
# Genes and Environment Initiative

- **Secretarial Initiative in FY2007 President's Budget**
- **2007-2010: \$40 million/yr**
  - ❑ \$26 million human genetic case-control studies
  - ❑ \$14 million environmental biology program
- **Environmental Biology Program – environment, diet, and activity level**
  - ❑ Sensor technology
  - ❑ Biological response indicators
  - ❑ Workshop – Spring, 2006

	2006	2007	2008	2009	2010	TOTAL
Appropriation	----	14	14	14	14	56
NIEHS	4	8	10	10	----	32

# Prioritize Diseases and Populations

- International patterns of disease (rates and geographical distribution)



ISAAC. *Lancet* 1998; 351:1225



# Prioritize Diseases and Populations

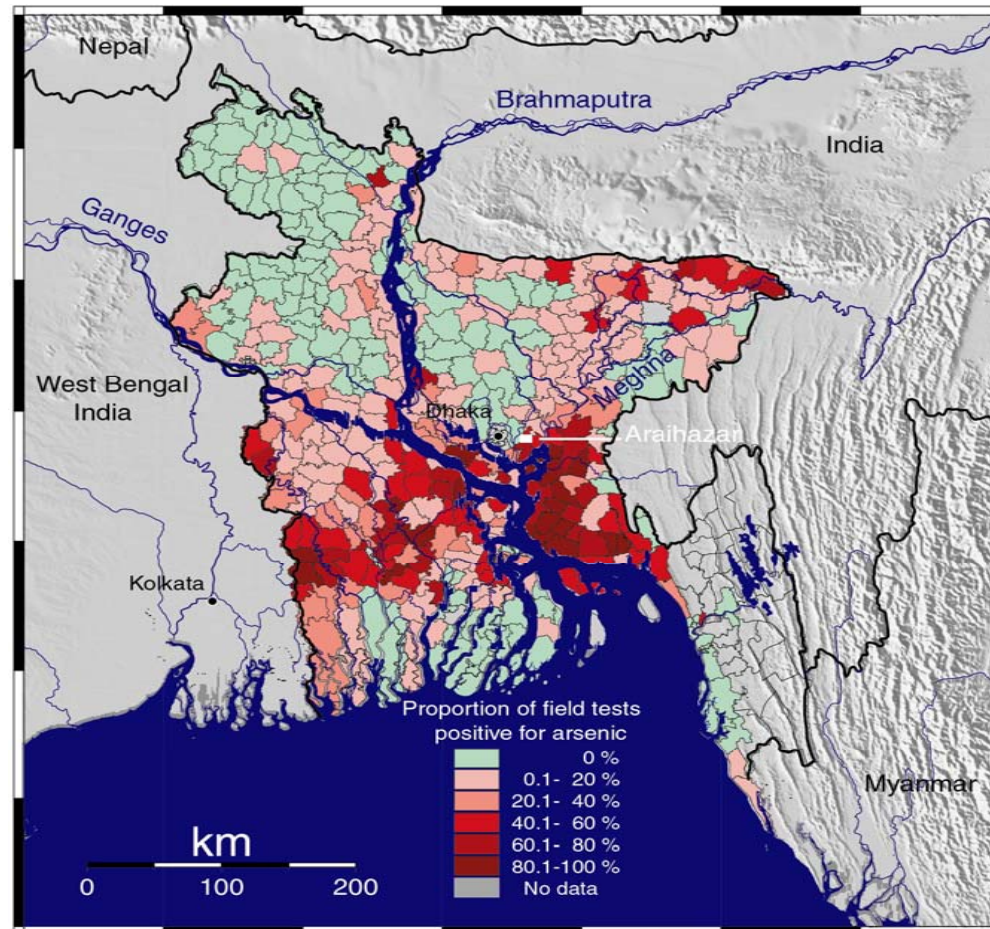
- International patterns of disease (rates and geographical distribution)
- Familial and twin studies (genetic vs. environmental contribution to disease phenotype)

Population	MZ concord (%)	DZ concord (%)	Heritability (%)
Finland (adults)	43	25	36
Australia (adults)	65	24	60-75
Norway (18-25 yr)	75	21	75
Sweden (16 yr)	76	45	79

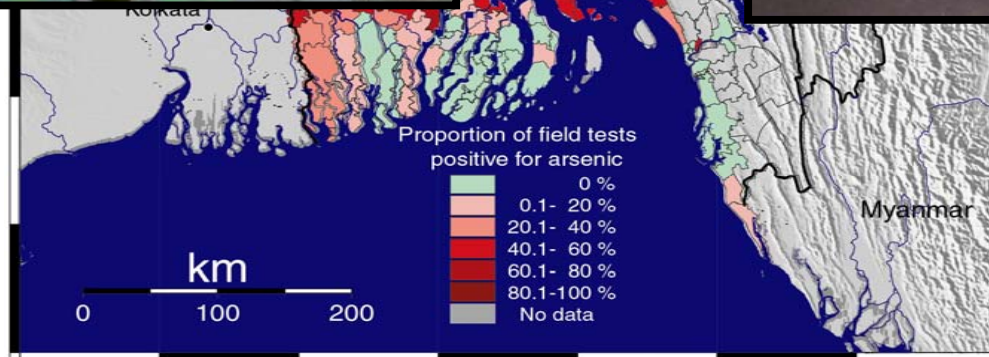
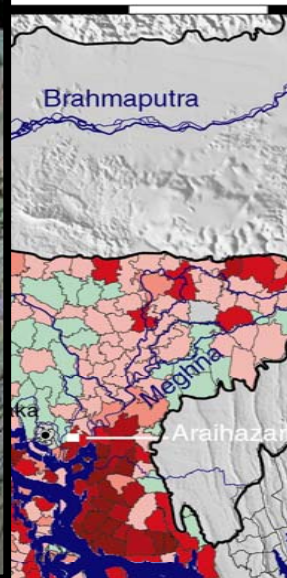
# **Prioritize Diseases and Populations**

- **International patterns of disease (rates and geographical distribution)**
- **Familial and twin studies (genetic vs. environmental contribution to disease phenotype)**
- **Populations exposed to high concentrations of common toxins**

# Global Environmental Health



# Global Environmental Health





# New Orleans Research Program



- Chronic airway disease
- Academic medical centers and the Dept of Public Health
- Family and community based study
- Investigate the role of microbial contamination on the exacerbation of chronic airway disease
- Federal and private partnerships

# Priorities for Program Development

- **Impact on Human Health and Disease**
  - Programmatic research focusing on complex human diseases
  - Enhance role of the clinical investigator
- **Environmental Genomics and Genetics**
  - Epigenetics
  - Comparative biology/genomics
  - Training in environmental genomics
- **Exposure Biology Program within GEI**
- **Global Environmental Health**